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(54) [original English:] **Title:** XANTHINE COMPOUND

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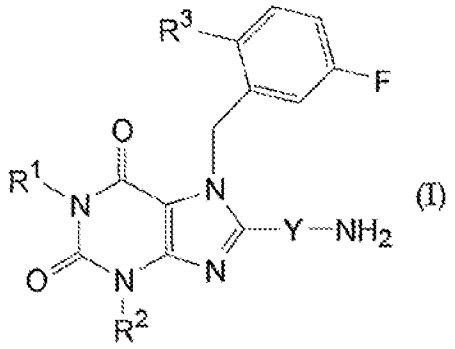

(57) [original English:] **Abstract:** A xanthine compound represented by the following formula (I), which has high DPP-IV inhibitory activity or is improved in safety, nontoxicity, etc.; a prodrug of the compound; or a pharmaceutically acceptable salt of either.

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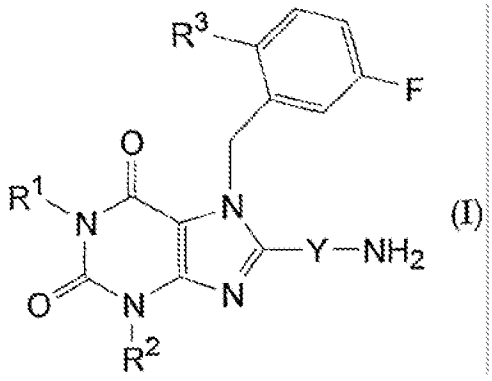
[see continuation sheet]

(57) Abstract:

A xanthine compound represented by the following formula (I), which has high DPP-IV inhibitory activity or is improved in safety, nontoxicity, etc.; a prodrug of the compound; or a pharmaceutically acceptable salt of either.




(I)

# DESCRIPTION

## XANTHINE COMPOUND

### Technical Field

The present invention relates to a novel xanthine compound useful as a pharmaceutical agent. In more detail, the present invention relates to a novel xanthine compound useful as a dipeptidyl peptidase-IV (DPP-IV) inhibitor, and further relates to a diabetes therapeutic agent having a novel xanthine compound useful as a dipeptidyl peptidase-IV (DPP-IV) inhibitor as the effective component.

### Prior Art

DPP-IV is a serine protease broadly distributed throughout the body, and is one type of dipeptidyl amino peptidase that hydrolyzes and releases N-terminal dipeptides. DPP-IV is also called a prolyl endopeptidase because of a particularly strong action on peptides in which the second amino acid from the N-terminal is proline. It is known that DPP-IV uses a variety of biological peptides participating in the endocrine system, neuroendocrine system, and immune function as a substrate. DPP-IV substrates include many physiologically active peptides such as: the pancreatic polypeptide family represented by pancreatic polypeptide (PP) and neuropeptide Y (NPY); the glucagon/VIP family represented by vasoactive intestinal polypeptide (VIP), glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP) and growth hormone releasing factor (GRF); and the chemokine family. DPP-IV is thus affected by activation/deactivation and metabolic stimulation (J. Langner and S. Ansorge, eds.: "Cellular Peptidases in Immune Functions and Disease 2", Advances in Experimental Medicine and Biology Vol. 477).

DPP-IV severs two amino acids (His-Ala) from the N-terminal of GLP-1. It is known that, although the severed peptides weakly bind to GLP-1 receptors, they act as antagonists without having an action to activate the receptor (L.B. Knudsen et al,

European Journal of Pharmacology, Vol. 318, p429-435, 1996). It is known that DPP-IV metabolizes GLP-1 in the blood extremely rapidly, and the active type GLP-1 concentration in the blood increases when DPP-IV is inhibited (T.J. Kieffer et al, Endocrinology, Vol. 136, p3585-3596, 1995). GLP-1 is a peptide that is excreted from the intestinal tract when ingesting sugar, and is major accelerator of the excretion of glucose-responsive pancreatic insulin. In addition, GLP-1 has an action to promote synthesis of insulin by the β-cells of the pancreas, as well as an action to promote β-cell proliferation. Further, it has been discovered that GLP-1 receptors are expressed in the gastrointestinal tract, liver, muscle and fatty tissues, and that GLP-1 acts on gastrointestinal tract activity, gastric acid excretion, glycogen synthesis and decomposition, and insulin dependent glucose uptake. Consequently, increasing the concentration of GLP-1 in the blood will have such effects as promoting the excretion of insulin depending on serum glucose level, improvement of pancreatic function, improvement of postprandial hyperglycemia, improvement of glucose tolerance anomalies, and improvement of insulin resistance, and therefore the development of a DPP-IV inhibitor effective for type II diabetes (non-insulin dependent diabetes) is being sought (A. Pederson et al, Diabetes Vol. 47, p1253-1258, 1998).

A variety of DPP-IV inhibitors have been reported, for example, in International Publication No. 02/02560 (WO 02/02560) it was reported that a xanthine compound having a piperidine ring and the like was effective as a DPP-IV inhibitor. Disclosed in International Publication No. 02/68420 (WO 02/68420) is xanthine derivative having a 3-aminopiperidine ring or a 1,2-cycloalkanediamino or the like at the 8$^{th}$ position of the xanthine, which is one of the characteristics of the present invention, that is effective as a DPP-IV inhibitor. However, compounds having a fluorine atom in position 5 on the benzene ring as well as a benzyl base substituted in position 2, as in the compound of the present invention, were not at all disclosed in the related literature.

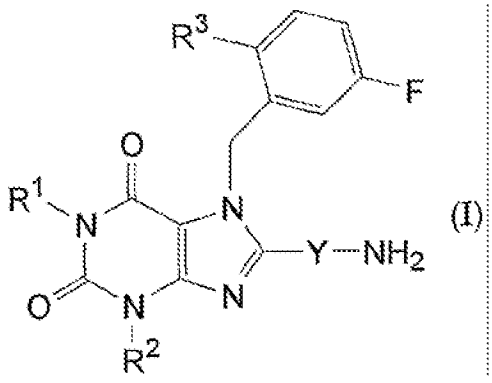
Moreover, it was reported in International Publication No. 02/24698 (WO 02/24698) that a xanthine compound is effective as a phosphodiesterase V inhibitor.

## Disclosure of the Invention

The problem to be solved by the present invention is to offer a compound that has high DPP-IV inhibition activity and that has an anti-diabetes action.

As a result of assiduous research to resolve the aforementioned problem, the present inventors initially synthesized a xanthine derivative with a chemical structure that in position 7 of the xanthine has a benzyl group having a fluorine atom in position 5 and a specified substitution group in position 2, and that in position 8 of the xanthine has either: (1) a 3-aminopiperidin-1-yl group, 3-aminopyrrolidine-1-yl group, or a 3-amino-hexahydroazepin-1-yl group; or (2) a (2-aminocycloalkyl)amino group. The present inventors discovered that this compound, a prodrug thereof or a pharmaceutically permissible salt of either (which may be abbreviated as the "compound of the present invention" as necessary hereinafter) has a superior DPP-IV inhibitory action as well as an anti-diabetes action, and thus the present invention was perfected. Specifically, the present invention relates to the following:

[1] A xanthine compound represented by the formula (I) below, a prodrug thereof, or a pharmaceutically permissible salt of either.




(I)

[In the formula, $R^1$ represents (1) a hydrogen atom, or (2) a $C_{1-6}$ alkyl group which may be substituted by one or multiple groups independently selected from $Ar^1$-X-or $A^1$;

$Ar^1$ represents an aryl group which may be substituted, an aromatic heterocyclic group which may be substituted, or an aliphatic heterocyclic group which may be substituted;

X represents a single bond, oxygen atom, -C(=O)-, -S(O)m-, or -S(O)m-NH-;

m represents 0, 1, or 2;

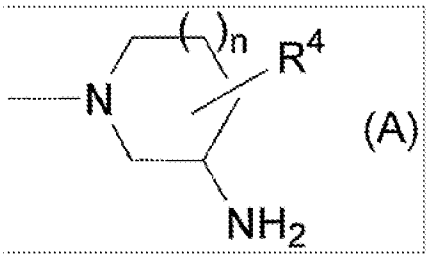
$A^1$ represents a halogen atom (which may be substituted with 1 to 3 of the same

carbon atoms), hydroxyl group, oxo group, cyano group, carboxy group, carbamoyl group which may be substituted with 1 or 2 of the same or different $C_{1-3}$ alkyl groups, $C_{1-6}$ alkoxy group, amino group, $C_{1-6}$ alkylamino group, di-$C_{1-6}$ alkylamino group, hydroxyimino group $C_{1-6}$ alkoxyimino group, acylamino group, $C_{1-6}$ alkoxycarbonylamino group, $C_{1-6}$ alkylthio group, $C_{1-6}$ alkylsulfinyl group, $C_{1-6}$ alkylsulfonyl group, $C_{1-6}$ alkoxycarbonyl group, arylsulfonyl group, $C_{3-6}$ cycloalkyl group, or $C_{1-6}$ alkylcarbonyl group;

$R^2$ represents a hydrogen atom, $C_{1-6}$ alkoxycarbonylmethyl group, or $C_{1-6}$ alkyl group;

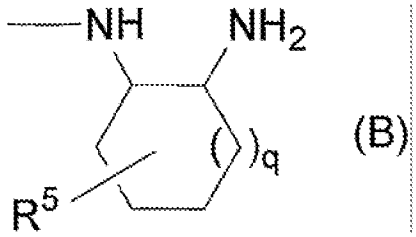
$R^3$ represents a chlorine atom, bromine atom, iodine atom, cyano group, carboxy group, amino group which may be substituted, $C_{1-6}$ alkyl group which may be substituted, $C_{1-6}$ alkylthio group which may be substituted, $C_{1-6}$ alkylsufinyl group which may be substituted, $C_{1-6}$ alkylsulfonyl group which may be substituted, $C_{2-6}$ alkenyl group, $C_{2-6}$ alkynyl group, $C_{1-6}$ alkylcarbonyl group which may be substituted, $C_{1-6}$ alkoxy group which may be substituted, or a carbamoyl group which may be substituted;

-Y-$NH_2$ represents a group represented by formula (A) below:




(A)

(In the formula, n represents 0, 1 or 2; if 1 or 2 are present, $R^4$ represents an independent hydrogen atom, halogen atom, hydroxyl group, caboxy group, oxo group, amino group which may be substituted, $C_{1-6}$ alkoxy group which may be substituted, $C_{1-6}$ alkyl group which may be substituted, phenyl group which may be substituted, or benzyl group which may be substituted; or if 2 are present, $R^4$ represents methylene or ethylene together with the above, and a bridging ring may be formed by bonding with 2 carbon atoms comprising a ring.); or by formula (B) below:




(In the formula, q represents 0, 1 or 2; if 1 or 2 are present, $R^5$ represents an independent hydrogen atom, halogen atom, hydroxyl group, caboxy group, oxo group, amino group which may be substituted, $C_{1-6}$ alkoxy group which may be substituted, $C_{1-6}$ alkyl group which may be substituted, $C_{1-6}$ alkoxycarbonyl group which may be substituted, carbamoyl group which may be substituted, phenyl group which may be substituted, or benzyl group which may be substituted; or if 2 are present, $R^5$ represents methylene or ethylene together with the above, and a bridging ring may be formed by bonding with 2 carbon atoms comprising a ring.)}

[2] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in item [1], wherein -Y-$NH_2$ is a group represented by formula (A) and n is 1 or 2, or -Y-$NH_2$ is a group represented by formula (B) and q is 1 or 2.

[3] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in item [1], wherein -Y-$NH_2$ is a group represented by formula (A) and n is 1, or -Y-$NH_2$ is a group represented by formula (B) and q is 1.

[4] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of items [1] to [3], wherein $R^2$ is a methyl group.

[5] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of items [1] to [4], wherein $R^4$ or $R^5$ is a hydrogen atom, halogen atom, $C_{1-6}$ alkyl group which may be substituted, or $C_{1-6}$ alkoxy group which may be substituted.

[6] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of items [1] to [5], wherein $R^3$ is a chlorine atom, bromine atom, iodine atom, methyl group, ethyl group, cyano group, trifluoromethyl group,

methoxy group, trifluoromethoxy group, or difluoromethoxy group.

[7] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of items [1] to [6], wherein $R^1$ is a $C_{1-6}$ alkyl group substituted by $Ar^1$-X-; $Ar^1$ is an aryl group which may be substituted, or an aromatic heterocyclic group which may be substituted; and X is a single bond, oxygen atom, -C(=O)-, or –S(O)m-.

[8] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of items [1] to [6], wherein $R^1$ is a $C_{1-2}$ alkyl group substituted by $Ar^1$-X-; $Ar^1$ is an aryl group which may be substituted, or an aromatic heterocyclic group which may be substituted; and X is a single bond, or -C(=O)-.

[9] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of items [1] to [6], wherein $R^1$ is an ethyl group substituted in position 2 by $Ar^1$-X-; $Ar^1$ is a phenyl group which may be substituted, a pyridyl group which may be substituted, quinolyl group which may be substituted, or an isoquinolyl group which may be substituted; and X is a single bond.

[10] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of items [1] to [6], wherein $R^1$ is a methyl group substituted by $Ar^1$-X-; $Ar^1$ is a phenyl group which may be substituted, a pyridyl group which may be substituted, quinolyl group which may be substituted, or an isoquinolyl group which may be substituted; and X is -C(=O)-.

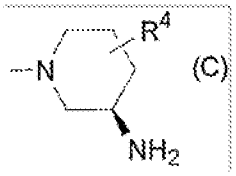
[11] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of items [1] to [10], wherein $Ar^1$ is a phenyl group which may be substituted.

[12] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of items [1] to [10], wherein $Ar^1$ is a pyridyl group which may be substituted.

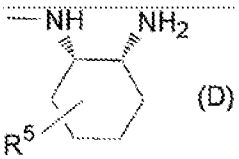
[13] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of items [1] to [6], wherein $R^1$ is a hydrogen atom or a methyl group.

[14] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of items [1] to [6], wherein $R^1$ is a methyl group.

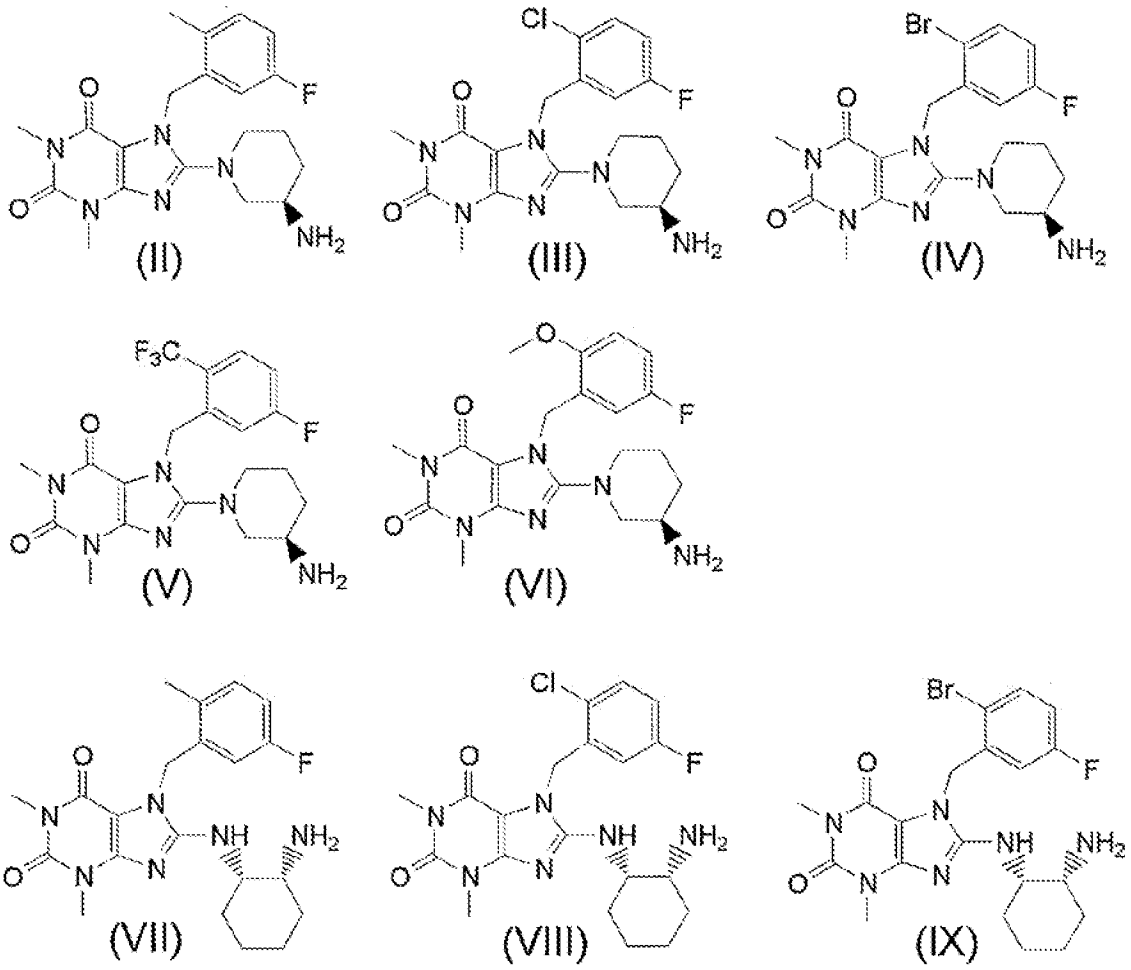
[15] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of items [1] to [14], wherein $-Y-NH_2$ is the following formula (C).




[16] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of items [1] to [14], wherein $-Y-NH_2$ is the following formula (D).




[17] A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in item [1] represented by the following formulae (II), (III), (IV), (V), (VI), (VII), (VIII) or (XI) below.




[18] A dipeptidyl peptidase IV inhibitor containing as an active ingredient the xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of items [1] to [17].

[19] A diabetes therapeutic agent containing as an active ingredient the xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of items [1] to [17].

[20] A diabetes therapeutic agent described in item [19] for concomitant use with other diabetes therapeutic agents.

Best mode for Carrying Out the Invention

The terminology used in the present Description will be explained in detail below.

Fluorine atoms, chlorine atoms, bromine atoms or iodine atoms may be cited as "halogen atoms".

Examples of the "$C_{1-6}$ alkyl group" include straight-chained or branched alkyl groups

having 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-ethylpropyl, and hexyl. Preferably, straight-chained or branched alkyl groups having 1 to 4 carbon atoms may be cited as the alkyl group. More preferably, methyl or ethyl may be cited as the alkyl group.

Examples of the "$C_{1-3}$ alkyl group" include straight-chained or branched alkyl groups having 1 to 3 carbon atoms such as methyl, ethyl, propyl, and isopropyl.

Methyl or ethyl may be cited as the "$C_{1-2}$ alkyl group".

Examples of the "$C_{2-6}$ alkenyl group" include straight-chained or branched alkenyl groups having 2 to 6 carbon atoms which have at least 1 double bond such as vinyl, propenyl, methylpropenyl, butenyl, or methylbutenyl. Preferably, straight-chained or branched alkenyl groups having 3 to 4 carbon atoms may be cited as the alkenyl group.

Examples of the "$C_{2-6}$ alkynyl group" include straight-chained or branched alkenyl groups having 2 to 6 carbon atoms which have at least 1 triple bond such as ethynyl, propynyl, methylpropynyl, butynyl, or methylbutynyl. Preferably, straight-chained or branched alkynyl groups having 3 to 4 carbon atoms may be cited as the alkynyl group.

Cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl may be cited as the "$C_{3-6}$ cycloalkyl group".

$C_{1-6}$ alkyloxy group and $C_{3-6}$ cycloalkyloxy group may be cited as the "$C_{1-6}$ alkoxy group". Preferably, straight-chained or branched alkoxy groups having 1 to 4 carbon atoms may be cited as the alkoxy group.

Examples of "$C_{1-3}$ alkoxy group" include $C_{1-3}$ alkyloxy group and cyclopropyloxy group.

The aforementioned $C_{1-6}$ alkyl groups may be cited as the $C_{1-6}$ alkyl group of the "$C_{1-6}$ alkylthio group", "$C_{1-6}$ alkylsulfinyl group", "$C_{1-6}$ alkylsulfonyl group" and "$C_{1-6}$ alkylcarbonyl".

The aforementioned $C_{1-6}$ alkyl groups may be cited as the $C_{1-6}$ alkyl group of the "$C_{1-6}$ alkylamino group", and "di-$C_{1-6}$ alkylamino group".

The aforementioned $C_{1-6}$ alkoxy groups may be cited as the $C_{1-6}$ alkoxy group of the "$C_{1-6}$ alkoxycarbonyl group", "$C_{1-6}$ alkoxycarbonylmethyl group", "$C_{1-6}$ alkoxycarbonyloxy group", "$C_{1-6}$ alkoxycarbonylamino group", or "$C_{1-6}$ alkoxyimino group".

The aforementioned $C_{1-3}$ alkoxy groups may be cited as the $C_{1-3}$ alkoxy group of the "$C_{1-3}$ alkoxycarbonyl group", "$C_{1-3}$ alkoxycarbonyloxy group", "$C_{1-3}$ alkoxycarbonylamino group", or "$C_{1-3}$ alkoxyimino group".

The aforementioned $C_{3-6}$ cycloalkyl groups may be cited as the $C_{3-6}$ cycloalkyl group of the"$C_{3-6}$ cycloalkyloxy group".

$C_{1-6}$ alkylcarbonyl groups such as acetyl and propionyl, and aroyl groups such as benzoyl and naphthoyl may be cited as the acyl of the "acylamino group".

Phenyl group, 1-naphthyl group, 2-naphthyl group, or indanyl group may be cited as the "aryl group". Preferable among these is the phenyl group.

Arylcarbonyl groups with 11 carbon atoms or less such as benzoyl, or naphthoyl may be cited as the "aroyl group".

The aforementioned aryl groups may be cited as the aryl group of the "aryloxy group", "arylsulfonyl group", "arylsulfonyloxy group", or "arylsulfonylamino group". Moreover, examples of the arylsulfonyl group and arylsulfonyloxy group include toluenesulfonyl group and toluensulfonyloxy group.

Monocyclic or bicyclic heterocyclic groups with 5 to 10 members containing 1 to 3 hetero atoms selected from 0 to 3 nitrogen atoms, 0 to 1 oxygen atoms, and 0 to 1 sulfur atoms (the sulfur atoms may be oxidized with 1 or 2 oxygen atoms.) may be cited as the "aromatic heterocyclic group". The aromatic hetero ring of the aromatic heterocyclic group may have a partially hydrogenised ring system as long as it is aromatic. Moreover, an oxo group may be substituted for 1 or multiple carbon atoms on the aromatic hetero

ring of the aromatic heterocyclic group as long as a stable structure can be made. Here, the bond positions of the aromatic heterocyclic group are not particularly limited, and bonding may occur on any nitrogen atom or carbon atom on the bondable ring.

Concrete examples of the aromatic hetero ring of the aromatic heterocyclic group include furan, thiophene, pyrrole, pyridine, indole, isoindole, purine, phthalazine, 4-oxo-3, 4-dihydrophthalazine, quinoline, 1,2-dihydroquinoline, tetrahydroquinoline, isoquinoline, 2-oxo-1,2-dihydroquinoline, tetrahydroisoquinoline, quinazoline, quinoxaline, naphthylidine, pyrazole, imidazole, triazole, pyrimidine, tetrahydropyrimidine, pyrazine, pyridazine, thiazole, oxazole, isoxazole, indolizine, chroman, isochroman, 4-oxo-4H-chromen, indazole, imidazopyrazine, imidazopyramidine, benzoimidazole, 2-oxo-2,3-dihydro-1H-benzoimidazole, benzothiazole, benzoisothiazole, benzoxazole, 2-oxo-2,3-dihydro-1H-benzoxazole, benzoisoxazole, benzofuran, 2,3-dihydrobenzofuran, benzothiophene, benzo[1,3] dioxole, 2-oxo-2,3-dihydro-benzo[1,4]dioxin, or 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine. Moreover, partially hydrogenated rings of the above rings, or rings with an oxo group substituted for 1 or multiple carbon atoms on the ring may also be cited.

Among these, pyridine, quinoline or isoquinoline are preferable, and pyridine is more preferable.

2-pyridyl group, 3-pyridyl group, or 4-pyridyl group may be cited as the pryidyl group.

Monocyclic or bicyclic heterocyclic groups with 5 to 10 members containing 1 to 3 hetero atoms selected from 0 to 3 nitrogen atoms, 0 to 1 oxygen atoms, and 0 to 1 sulfur atoms (the sulfur atoms may be oxidized with 1 or 2 oxygen atoms.) may be cited as the "aliphatic heterocyclic group". The aliphatic heterocyclic group may contain a partially

unsaturated bond. Moreover, an oxo group may be substituted for 1 or multiple carbon atoms on the ring of the aliphatic heterocyclic group as long as a stable structure can be made. Here, the bond positions of the aliphatic heterocyclic group are not particularly limited, and bonding may occur on any nitrogen atom or carbon atom on the bondable ring.

Concrete examples of aliphatic hetero rings of the aliphatic heterocyclic group include pyrrolidine, 2-oxopyrrolidine, pyrroline, piperidine, piperadine (the nitrogen atoms of the piperadine may be substituted with methyl or ethyl), 2-oxoimidazolidine, 2,4-dioxoimidazolidine, morpholine, thiomorpholine, thiomorpholine-1-oxide, or thiomorpholine-1,1-dioxide.

Examples of substitution groups for the $C_{1-6}$ alkyl group which may be substituted, $C_{2-6}$ alkenyl group which may be substituted, $C_{3-6}$ cycloalkyl group which may be substituted, $C_{1-6}$ alkoxy group which may be substituted, $C_{1-6}$ alkylcarbonyl group which may be substituted, $C_{1-6}$ alkylthio group which may be substituted, $C_{1-6}$ alkylsulfinyl group which may be substituted, $C_{1-6}$ alkylsulfonyl group which may be substituted, phenyl group which may be substituted, and benzyl group which may be substituted include: halogen atoms (1 to 3 may be substituted for the same carbon atom), hydroxyl group, cyano group, carboxy group, $C_{2-6}$ alkenyl group, $C_{2-6}$ alkynyl group, $C_{3-6}$ cycloalkyl group, $C_{1-6}$ alkoxy group, $C_{1-6}$ alkylcarbonyl group, $C_{1-6}$ alkoxycarbonyl group, carbamoyl group which may be substituted, amino group, $C_{1-6}$ alkylamino group, di-$C_{1-6}$ alkylamino group, aliphatic heterocyclic group, acylamino group, $C_{1-6}$ alkylsulfonylamino group, arylsulfonylamino group, $C_{1-6}$ alkoxycarbonylamino group, $C_{1-6}$ alkylthio group, $C_{1-6}$ alkylsufinyl group, $C_{1-6}$ alkylsulfonyl group, and arylsulfonyl group. One or multiple of these substitution groups may be present. Further, the aforementioned $C_{1-6}$ alkyl group which may be substituted may also be cited as a substitution group of the phenyl group which may be substituted and the benzyl group which may be substituted.

Examples of substitution groups for the amino group which may be substituted include $C_{1-6}$ alkyl group which may be substituted, $C_{3-6}$ cycloalkyl group which may be

substituted, $C_{1-6}$ alkylcarbonyl group, aroyl group, $C_{1-6}$ alkoxycarbonyl group, $C_{1-6}$ alkylsulfonyl group, and arylsulfonyl group; and 1 or 2 of these substitution groups may be present.

Concrete examples of substituted amino groups include methylamino group, ethylamino group, dimethylamino group, acetylamino group, propionylamino group, benzoylamino group, naphthoylamino group, methoxycarbonylamino group, ethoxycarbonylamino group, tert-butoxycarbonylamino group, methylsulfonylamino group, ethylsulfonylamino group.

Examples of the substitution group of the carbamoyl group which may be substituted include $C_{1-6}$ alkyl group which may be substituted, $C_{3-6}$ cycloalkyl group, $C_{1-6}$ alkyl group substituted with $C_{3-6}$ cycloalkyl group, $C_{1-6}$ alkylcarbonyl group, and aroyl group; and 1 or 2 of these substitution groups may be present.

Moreover, a substitution group comprising 2 of the carbamoyl groups may be bonded to form an aliphatic hetero ring that may contain carbon, nitrogen, oxygen or sulfur such as pyrrolidine, piperidine, morpholine, thiomorpholine, thiomorpholine oxide, thiomorpholine dioxide, or piperazine (the nitrogen atom of the piperazine may be substituted with methyl or ethyl).

Concrete examples of substituted carbamoyl groups include monomethylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, N-propylcarbamoyl, N-isopropylcarbamoyl, N-ethyl-N-methylcarbamoyl, N-methyl-N-propylcarbamoyl, N-cyclopropylcarbamoyl, N-cyclopropylmethylcarbamoyl, acetylcarbamoyl, benzoylcabamoyl, pyrrolidinocarbonyl, piperidinocarbonyl, and morpholinocarbonyl.

Examples of aryl group which may be substituted or aromatic heterocyclic groups which may be substituted include halogen atoms, hydroxyl group, carboxy group, cyano group, amino group, nitro group, $C_{1-6}$ alkyl group which may be substituted (here, halogen atoms, $C_{1-3}$ alkyl group, $C_{1-3}$ alkoxycarbonyl group, $C_{1-3}$ alkoxycarbonyloxy group or carboxy group may be cited as the substituted group), $C_{2-6}$ alkenyl group, $C_{2-6}$

alkynyl group, $C_{3-6}$ cycloalkyl group, $C_{1-6}$ alkoxy group which may be substituted, $C_{3-6}$ cycloalkyloxy group, $C_{1-6}$ alkylcarbonyl group, $C_{1-6}$ alkylthio group, $C_{1-6}$ alkylsulfinyl group, $C_{1-6}$ alkylsulfonyl group, amino groups which may be substituted with 1 to 2 of the same or different $C_{1-3}$ alkyl group, $C_{1-6}$ alkylcarbonylamino group, $C_{1-6}$ alkoxycarbonylamino group, $C_{1-6}$ alkylsulfonylamino group, carbamoyl group, sulfamoyl group, ureide group, thioureide group, aminocarbonyloxy group, aminosulfonylamino group (here, the carbamoyl group, sulfamoyl group, ureide group, thioureide group, aminocarbonyloxy group, aminosulfonylamino group may be substituted with 1 to 2 of the same or different $C_{1-3}$ alkyl group), $C_{1-6}$ alkoxycarbonylmethylamino group, $C_{1-6}$ alkylcarbamoylmethylamino group, $C_{1-6}$ alkoxycarbonylaminocarbonylamino group, carboxymethoxy group, cyanomethoxy group, $C_{1-6}$ alkoxycarbonylmethyloxy group, cyanomethylamino group, N-methyl-N-cyanomethylamino group, aryl group, aryloxy group, and arylsulfonyloxy group, 2-oxoimidazolinyl group, 3-methyl-2-oxoimidazolinyl group, 3-methyl-2,4-dioxoimidazolidinyl group, 2-oxotetrahydropyrimidinyl group, or 3-methyl-2-oxotetrahydropyrimidinyl; and one or multiple of these substitution groups may be substituted. The substitution position of the substitution group is not particularly limited, and may be freely substituted on the nitrogen atoms or carbon atoms on the bondable ring.

Examples of substitution groups for the aliphatic heterocyclic groups which may be substituted include hydroxyl group, carboxy group, $C_{1-3}$ alkyl group, $C_{1-3}$ alkoxy group, $C_{1-3}$ alkylcarbonylamino group, $C_{1-3}$ alkylsulfonylamino group, amino group which may be substituted with 1 or 2 of the same or different $C_{1-3}$ alkyl groups, and carbamoyl group which may be substituted with 1 or 2 of the same or different $C_{1-3}$ alkyl groups; and one or multiple of these substitution groups may be substituted. The substitution position of the substitution group is not particularly limited, and may be freely substituted on the nitrogen atoms or carbon atoms on the bondable ring.

For $Ar^1$, the same substitution groups as those of the aforementioned aryl group which may be substituted or aromatic heterocyclic group which may be substituted may

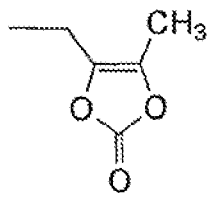
be cited for the substitution group of the phenyl group which may be substituted, pyridinyl group which may be substituted, quinolyl group which may be substituted and isoquinolyl group which may be substituted; and one or multiple of these substitution groups may be substituted. The substitution position on the $Ar^1$ of the substitution group and the bonding position of the $Ar^1$ to bond with X are not particularly limited, and may be freely substituted or bonded on the bondable nitrogen atoms or carbon atoms on the ring.

Preferably the ortho position or meta position of the $Ar^1$ may be cited as the substitution position of the phenyl group which may be substituted.

Fluorine atom, chlorine atom, bromine atom, iodine atom, methyl group, ethyl group, cyano group, trifluoromethyl group, methoxy group, trifluoromethoxy group, difluoromethoxy group, amino group, methylthio group,methylsulfinyl group, or methylsulfonyl group are preferable as the substitution group of the phenyl group which may be substituted for $Ar^1$.

Compounds that easily hydrolyze in the body and reproduce the xanthine compound of the present invention, specifically, for example, compounds in which the amino group of the xanthine compound $-NH_2$ is derived from –NHQ may be cited as the "prodrug". Here, Q has the following meaning:

(1)



(2) $-COR^{17}$

(3) $-COO-CR^{18}(R^{19})-OCOR^{20}$

(4) $-COOR^{21}$

[In the formula, $R^{17}$ represents hydrogen atom, $C_{1-6}$ alkyl group, or a phenyl group or an aryl group which may be substituted. $R^{18}$ and $R^{19}$ represent independent hydrogen atoms or $C_{1-6}$ alkyl groups. $R^{20}$ represents a hydrogen atom, $C_{1-6}$ alkyl group, the aforementioned aryl group or benzyl group. $R^{21}$ represents $C_{1-6}$ alkyl group or benzyl group.]

Group (1) and group (3) are preferable for Q. For group (3), it is preferable that $R^{18}$ be a hydrogen atom, $R^{19}$ be a hydrogen atom, methyl or ethyl, and $R^{20}$ be a hydrogen atom, methyl or ethyl. These compounds may be manufactured following normal methods (J. Med. Chem. 35, 4727 (1992), WO 01/40180, etc.). Moreover, the prodrug may be one that changes to the original compound under such physiological conditions as described on pages 163 to 198 of "Development of Pharmaceutical Products, Vol. 7, Molecular Design", published by Hirokawa Shoten in 1990.

Examples of "pharmaceutically permissible salts" include inorganic salts such as hydrochloride, hydrobromide, sulfate, phosphate, and nitrate, or organic salts such as acetate, propionate, succinate, lactate, malate, tartrate, citrate, maleate, fumarate, methanesulfonate, p-toluenesulfonate or ascorbate.

Additionally, the present invention also includes a hydrate or an ethanolic solvate of a xanthine compound, the prodrug thereof or a pharmaceutically permissible salt of either. Further, the present invention also encompasses all tautomers, all existing stereoisomeric forms, and all crystalline forms of the xanthine compound.

The following 3-aminopiperidin compounds may be cited as preferable examples of the xanthine compound of the present invention.

(1) 1-(methoxycarbonylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(2) 1-(ethoxycarbonylmethyl)-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(3) 1-methyl3-(methoxycarbonylmethyl)-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(4) 1-methyl-3-(ethoxycarbonylmethyl)-7-(2-chloro-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(5) 1-(benzyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(6) 1-(3-phenylpropyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(7) 1-(2-hydroxyethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(8) 1-(2-methoxyethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(9) 1-[2-(dimethylamino)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(10) 1-[2-(2,4,6-trimethylphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(11) 1-[2-(2,4-dichlorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(12) 1-(2-thiophen-2-yl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(13) 1-(2-thiophen-3-yl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(14) 1-[2-(4-tert-butylphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(15) 1-[2-(2-fluorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(16) 1-[2-(2-methylphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(17) 1-[2-(3-methylphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(18) 1-[2-(1-naphthyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(19) 1-[2-(2-naphthyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-

aminopiperidin-1-yl)-xanthine

(20) 1-(4-phenylbutyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(21) 1-[2-(3-trifluoromethylphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(22) 1-[2-(pyridin-2-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(23) 1-[2-(pyrrol-1-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(24) 1-[2-([1,2,3] triazol-1-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(25) 1-[2-(pyridin-4-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(26) 1-(3-buten-1-yl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(27) 1-(4-pentin-1-yl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(28) 1-[2-(4-methylazol-5-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(29) 1-[2-(3-bromophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(30) 1-[2-(3-chlorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(31) 1-((E)-2-phenylvinyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(32) 1-[2-(2-chlorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(33) 1-[2-(2-trifluoromethylphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(34) 1-[2-(2-bromophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(35) 1-[2-(3-fluorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(36) 1-[2-(3-nitrophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(37) 1-[2-(4-methylphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(38) 1-[2-(4-hydroxyphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(39) 1-[2-(3-hydroxyphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(40) 1-[(methoxycarbonyl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(41) 1-[2-(methoxycarbonyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(42) 1-phenyl-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(43) 1-[2-(3,5-difluorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(44) 1-[2-(2,6-difluorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(45) 1-[2-(thiophen-3-yl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(46) 1-[2-(3-cyanomethoxyphenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(47) 1-[2-(3-benzyloxyphenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(48) 1-[2-(3-phenylsulfonyloxyphenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-

fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(49) 1-[2-(3-hydroxyphenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(50) 1-[2-(3,5-dimethoxyphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(51) 1-[3-(methoxycarbonyl)propyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(52) 1-{2-[4-(ethoxycarbonyl)phenyl]ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(53) 1-(phenylsulfanylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(54) 1-(phenylsufinylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(55) 1-(2-methoxycarbonyl-2-propen-1-yl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(56) 1-[(pyridin-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(57) 1-[2-(3-phenyloxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(58) 1-[2-(3-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(59) 1-(2-{3-[bis(methanesulfonyl)-amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(60) 1-[2-(2-bromo-5-dimethylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(61) 1-[2-(3-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(62) 1-[2-(3-methoxycargbonylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-

5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(63) 1-[2-(3-acetylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(64) 1-[2-(3-{[(ethoxycarbonylamino)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(65) 1-[2-(3-cyanomethylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(66) 1-[(thiazol-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(67) 1-[(isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(68) 1-[(isoquinolin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(69) 1-[(benzo[d]isothiazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(70) 1-[(benzo[d]isoxazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(71) 1-[(pyridin-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(72) 1-[(pyridin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(73) 1-[(isoxazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(74) 1-[(1-naphthyl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(75) 1-[(aminocarbonyl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(76) 1-[2-(3-methanesulfonylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-

fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(77) 1-[2-(2-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(78) 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(79) 1-[2-{3-[(methylamino)thiocarbonylamino]-phenyl}- 2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(80) 1-[2-(2-acetylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(81) 1-[(6-methyl-pyridin-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(82) 1-[(1-methyl-1H-indazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(83) 1-(2-{3-[(methoxycarbonyl)methylamino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(84) 1-cyanomethyl-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(85) 1-[2-(2-hydroxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(86) 1-[2-(2-methanesulfonyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(87) 1-[2-{2-[(methoxycarbonyl)methoxy]-phenyl}-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(88) 1-[2-(2-cyanomethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(89) 1-(2-{3-[(methylaminocarbonyl)methoxy]-phenyl}-2-oxo-ethyl)-3-methyl-7-

(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(90) 1-(2-{3-[(aminocarbonyl)methoxy]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(91) 1-(2-{3-[(dimethylaminocarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(92) 1-(4-oxo-4H-chromen-3-yl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(93) 1-[(3-methyl-pyridin-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(94) 1-[(5-methyl-pyridin-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(95) 1-[(4-methyl-pyridin-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(96) 1-[(quinolin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(97) 1-[(quinolin-8-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(98) 1-[(5-nitro-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(99) 1-[(2-oxo-1,2-dihydro-quinolin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(100) 1-[(5-amino-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(101) 1-[2-(3-aminosulfonyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(102) 1-(2-phenoxy-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-

aminopiperidin-1-yl)-xanthine
(103) 1-carboxymethyl-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(104) 1-(3-carboxy-propyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(105) 1-[2-(4-carboxy-phenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(106) 1-(2-phenyl-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(107) 1-[2-(3-amino-phenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(108) 1-[2-(pyrrolidin-1-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(109) 1-[2-(piperidin-1-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(110) 1-[2-(morpholin-4-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(111) 1-[2-(piperazin-1-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(112) 1-[2-(4-methyl-piperazin-1-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(113) 1-(3-hydroxypropyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(114) 1-(3-methoxypropyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(115) 1-(3-ethoxypropyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(116) 1-[3-(dimethylamino)propyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(117) 1-[3-(pyrrolidin-1-yl)propyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(118) 1-[3-(morpholin-4-yl)propyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(119) 1-[3-(piperazin-1-yl)propyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(120) 1-[3-(4-methyl-piperazin-1yl)propyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(121) 1-(pyrrolidin-1-yl-carbonylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(122) 1-(piperidin-1-yl-carbonylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(123) 1-(morpholin-4-yl-carbonylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(124) 1-[2-(3-fluoro-4-hydroxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(125) 1-[2-(4-methoxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(126) 1-[2-(4-ethoxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(127) 1-(2-{4-[(carboxymethyl)oxy]-phenyl}-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(128) 1-[2-(2-fluoro-5-hydroxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(129) 1-[2-(3-methoxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(130) 1-{2-[3-(carboxymethyloxy)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(131) 1-(2-{3-[(ethoxycarbonyl)methyloxy]-phenyl}-ethyl)-3-methyl-7-(2-methyl-

5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(132) 1-[2-(2-hydroxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(133) 1-[2-(2-methoxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(134) 1-{2-[2-(carboxymethyloxy)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(135) 1-(2-{2-[(methoxycarbonyl)methyloxy]-phenyl}-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(136) 1-[2-(4-hydroxymethyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(137) 1-{2-[4-(methoxycarbonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(138) 1-{2-[4-(carboxymethyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(139) 1-(2-{4-[(methoxycarbonyl)methyl]-phenyl}-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(140) 1-{2-[4-(2-carboxy-ethyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(141) 1-(2-{4-[2-(methoxycarbonyl)-ethyl]-phenyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(142) 1-[2-(3-methyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(143) 1-[2-(3-carboxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(144) 1-{2-[3-(ethoxycarbonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(145) 1-{2-[3-(carboxymethyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(146) 1-(2-{3-(methoxycarbonyl)methyl-phenyl}-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(147) 1-{2-[3-(2-carboxy-ethyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(148) 1-(2-{3-[2-(methoxycarbonyl)-ethyl]-phenyl}-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(149) 1-[2-(2-methyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(150) 1-[2-(2-carboxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(151) 1-{2-[2-(methoxycarbonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(152) 1-[2-(4-fluoro-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(153) 1-[2-(4-chloro-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(154) 1-[2-(4-bromo-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(155) 1-[2-(4-cyano-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(156) 1-[2-(4-trifluoromethoxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(157) 1-[2-(4-methylsulfanyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(158) 1-[2-(4-methylsulfinyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(159) 1-[2-(4-methylsulfonyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-

fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(160) 1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(161) 1-[2-(4-amino-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(162) 1-(2-{4-[(methylcarbonyl)amino]-phenyl}-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(163) 1-(2-{4-[(methylsulfonyl)amino]-phenyl}-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(164) 1-{2-[4-(aminocarbonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(165) 1-{2-[4-(methylaminocarbonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(166) 1-{2-[4-(dimethylaminocarbonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(167) 1-{2-[4-(aminosulfonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(168) 1-{2-[4-(methylaminosulfonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(169) 1-{2-[4-(dimethylaminosulfonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(170) 1-[3-(ethoxycarbonyl)-propyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(171) 1-[2-(3,4-dimethyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(172) 1-[2-(2-fluoro-5-chloro-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(173) 1-[2-(3,5-dimethoxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(174) 1-[2-(naphthalen-2-yl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(175) 1-[2-(pyrilidin-3-yl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(176) 1-[4-phenyl-butyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(177) 1-(2-phenylsulfanyl-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(178) 1-(2-phenylsulfinyl-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(179) 1-(2-phenylsulfonyl-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(180) 1-[2-(3-fluoro-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(181) 1-[2-(3-chloro-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(182) 1-[2-(3-bromo-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(183) 1-[2-(3-methyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(184) 1-[2-(3-trifluoromethyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(185) 1-[2-(2-methyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(186) 1-[2-(3-difluoromethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(187) 1-[2-(3-trifluoromethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(188) 1-[2-(3-ethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-

8-(3-aminopiperidin-1-yl)-xanthine
(189) 1-[2-(3-isopropyloxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(190) 1-[2-(3-cyclopropyloxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(191) 1-[2-(3-cyclopentyloxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(192) 1-[2-(3-cyclopropylmethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(193) 1-{2-[3-(2,2,2-trifluoroethoxy)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(194) 1-[2-(4-hydroxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(195) 1-{2-[3-(methylcarbonylamino)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(196) 1-{2-[3-(aminocarbonylamino)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(197) 1-{2-[3-(methylaminocarbonylamino)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(198) 1-{2-[3-(dimethylaminocarbonylamino)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(199) 1-{2-[3-(methylsulfonylamino)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(200) 1-{2-[3-(aminosulfonyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(201) 1-{2-[3-(methylaminosulfonyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(202) 1-{2-[3-(dimethylaminosulfonyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(203) 1-[2-(3-ethynyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(204) 1-[2-(3-cyano-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(205) 1-{2-[3-(aminocarbonyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(206) 1-{2-[3-(methylaminocarbonyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(207) 1-{2-[3-(dimethylaminocarbonyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(208) 1-{2-[3-(methylsulfanyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(209) 1-{2-[3-(methylsulfinyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(210) 1-{2-[3-(methylsulfonyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(211) 1-[2-(3,5-dimethyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(212) 1-[2-(3-fluoro-5-methyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-

fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(213) 1-[2-(pyrridin-3-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(214) 1-[2-(furan-2-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(215) 1-[2-(thiophen-2-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(216) 1-[2-(thiazol-2-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(217) 1-[2-(thiazol-5-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(218) 1-[2-(thiazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(219) 1-(2-phenyl-2-hydroxyimino-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(220) 1-(2-phenyl-2-methoxyimino-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(221) 1-(2-oxo-propyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(222) 1-(2-oxo-butyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(223) 1-(3-methyl-2-oxo-butyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(224) 1-(2-cyclopropyl-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(225) 1-(2-cyclohexyl-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(226) 1-(3-dimethylamino-2,3-dioxo-propyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(227) 1-[3-(piperidin-1-yl)-2,3-dioxo-propyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(228) 1-(2-phenyl-2-hydroxy-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(229) 1-(2-phenyl-2-hydroxy-propyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(230) 1-(2-phenyl-2-methoxy-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(231) 1-[(quinazolin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(232) 1-[(5-methyl-isoxazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(233) 1-[(oxazol-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(234) 1-[(1H-indazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(235) 1-[(5-fluoro-benzo[d]isothiazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(236) 1-[(5-fluoro-benzo[d]isoxazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(237) 1-[(5-methyl-benzo[d]isoxazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(238) 1-[(5-methyl-benzo[d]isothiazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(239) 1-(2-cyclohexyl-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(240) 1-[2-(2-difluoromethoxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(241) 1-[2-(2-difluoromethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-

fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(242) 1-[2-(2-trifluoromethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(243) 1-[2-(indan-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(244) 1-[2-(benzo[1,3]dioxol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(245) 1-[2-(2,2-difluoro-benzo [1,3] dioxol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(246) 1-[2-(naphtho-1-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(247) 1-[2-(2-isopropyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(248) 1-[2-(2-cyclopropyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(249) 1-[2-(2-cyclopentyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(250) 1-[2-(2-phenyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(251) 1-[2-(2-cyclopentylmethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(252) 1-(3-phenyl-2-oxo-propyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(253) 1-(3-phenyl-3-oxo-propyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(254) 1-[2-(2-methylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(255) 1-{2-[2-(N-cyanomethyl-N-methyl-amino)-phenyl]-2-oxo-ethyl}-3-methyl-7-

(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(256) 1-[2-(2-cyanomethylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(257) 1-(2-{2-[(methoxycarbonyl)methylamino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(258) 1-[2-(2-methylsulfonylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(259) 1-[2-(3-methylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(260) 1-{2-[3-(N-cyanomethyl-N-methyl-amino)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(261) 1-(2-{3-[(dimethylamino)sulfonylamino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(262) 1-(2-{3-[(morpholin-4-yl)sulfonylamino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(263) 1-[2-(3-aminosulfonylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(264) 1-[2-(3-ethylsulfonylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(265) 1-[2-(3-isopropylsulfonylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(266) 1-{2-[3-(2-oxo-imidazolin-1-yl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(267) 1-{2-[3-(3-methyl-2-oxo-imidazolidine-1-yl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(268) 1-{2-[3-(3-methyl-2,5-dioxo-imidazolidine-1-yl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(269) 1-{2-[3-(3-methyl-2,4-dioxo-imidazolidine-1-yl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(270) 1-[(1-methyl-2-oxo-1,2-dihydro-quinolin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(271) 1-[(2-oxo-1,2-dihydro-quinazolin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(272) 1-[(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(273) 1-[(2-cyano-naphthalen-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(274) 1-[(6-cyano-naphthalen-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(275) 1-[(5-cyano-naphthalen-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(276) 1-[(8-methyl-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(277) 1-[(5-cyano-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(278) 1-[(5-aminocarbonyl-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(279) 1-[(5-aminosulfonyl-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(280) 1-[(5-methylsulfonyl-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(281) 1-[(5-methylsulfonylamino-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(282) 1-[(5-methoxy-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(283) 1-[(6-methoxy-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(284) 1-[(7-methylsulfonylamino-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(285) 1-[(7-cyano-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(286) 1-[(7-aminocarbonyl-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(287) 1-[2-(2-aryloxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(288) 1-[2-(3-{[(morpholin-4-yl)carbonyl]methoxy}-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(289) 1-[2-(3-carboxymethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(290) 1-[2-(3-methylsulfanylmethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(291) 1-[2-(3-methylsulfinylmethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(292) 1-[2-(3-methylsulfonylmethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(293) 1-[2-(2-oxo-2,3-dihydro-benzoxazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(294) 1-[2-(2-oxo-2,3-dihydro-1H-benzoimidazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(295) 1-[2-(1-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(296) 1-[2-(1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzoimidazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(297) 1-[2-(1H-benzoimidazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(298) 1-[2-(2-methyl-1H-benzoimidazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(299) 1-[2-(benzoxazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(300) 1-[2-(2-methyl-benzoxazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(301) 1-[2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxadin-5-yl-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(302) 1-[2-(benzo[1,3]dioxol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

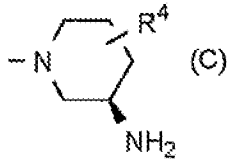
(303) 1-(1-methoxycarbonyl-1-phenyl-methyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(304) 1-(1-carboxy-1-phenyl-methyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(305) 1-(1-aminocarbonyl-1-phenyl-methyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(306) 1-(1-methoxycarbonyl-2-phenyl-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(307) 1-(1-carbonyl-2-phenyl-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(308) 1-(1-aminocarbonyl-2-phenyl-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(309) 1-[(benzofuran-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(310) 1-[(2,3-dihydro-benzofuran-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(311) 1-[2-(2-amino-3-cyano-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(312) 1-[2-(2-amino-3-fluoro-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(313) 1-(1-methyl-2-phenyl-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(314) 1-[2-oxo-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxadin-8-yl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(315) 1-[2-oxo-2-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxadin-8-yl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(316) 1-[(2-oxo-2H-chromen-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-

8-(3-aminopiperidin-1-yl)-xanthine
(317) 1-[(1-oxo-1,2-dihydro-isoquinolin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(318) 1-[(2-methyl-1-oxo-1,2-dihydro-isoquinolin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(319) 1-[(4-oxo-3,4-dihydro-phthalazin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(320) 1-[(3-methyl-4-oxo-3,4-dihydro-phthalazin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(321) 1-[([1,5]naphthylidin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(322) 1-[([1,7]naphthylidin-8-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(323) 1-[(quinolin-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(324) 1-[(isoquinolin-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(325) 1-{2-oxo-2-[3-(2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(326) 1-{2-oxo-2-[3-(3-methyl-2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(327) 1-(2-phenyl-2-oxoethyl)-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(328) 1-(2-phenyl-2-oxoethyl)-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

(329) 1-[(isoquinolin-1-yl)methyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(330) 1-[(isoquinolin-1-yl)methyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(331) 1-[2-(pyridin-2-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(332) 1-[2-(pyridin-2-yl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(333) 1-[2-(pyridin-2-yl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(334) 1-[2-(2-naphtyl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(335) 1-[2-(2-naphtyl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(336) 1-(2-phenyl-2-oxoethyl)-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(337) 1-(2-phenyl-2-oxoethyl)-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(338) 1-[2-(2-methoxyphenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(339) 1-[2-(2-methoxyphenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(340) 1-[2-(3-methoxyphenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(341) 1-[2-(3-methoxyphenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(342) 1-[2-(2-chlorophenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(343) 1-[2-(2-chlorophenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-

(3-aminopiperidin-1-yl)-xanthine
(344) 1-[2-(3-chlorophenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(345) 1-[2-(3-chlorophenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(346) 1-(2-phenylethyl)-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(347) 1-(2-phenylethyl)-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(348) 1-[2-(2-bromophenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(349) 1-[2-(2-cyanophenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(350) 1-[2-(2-methoxyphenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine
(351) 1-[2-(3-methoxyphenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)-xanthine

The preferable compounds among (1) to (351) above are the piperidine compounds in which the position 3 amino group of the 3-aminopiperidine has the absolute configuration expressed by the formula (C) below.



(C)

In addition, the following cycloalkanediamine compounds may also be cited as preferable examples of xanthine compounds of the present invention.
(352) 1,3-dimethyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]-xanthine

(353) 1,3-dimethyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(354) 1,3-dimethyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(355) 1-[2-(phenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(356) 1-[2-(2-fluorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(357) 1-[2-(2-chlorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(358) 1-[2-(2-bromophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(359) 1-[2-(2-cyanophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(360) 1-[2-(2-methoxyphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(361) 1-[2-(3-fluorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(362) 1-[2-(3-chlorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(363) 1-[2-(3-bromophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(364) 1-[2-(3-cyanophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(365) 1-[2-(3-methoxyphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(366) 1-[2-(phenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(367) 1-[2-(2-fluorophenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-

[(2-aminocyclohexyl)amino]xanthine
(368) 1-[2-(2-chlorophenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(369) 1-[2-(2-bromophenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(370) 1-[2-(2-cyanophenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(371) 1-[2-(2-methoxyphenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(372) 1-[2-(3-fluorophenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(373) 1-[2-(3-chlorophenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(374) 1-[2-(3-bromophenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(375) 1-[2-(3-cyanophenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(376) 1-[2-(3-methoxyphenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(377) 1-(methoxycarbonylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(378) 1-(ethoxycarbonylmethyl)-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(379) 1-methyl-3-(methoxycarbonylmethyl)-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(380) 1-methyl-3-(ethoxycarbonylmethyl)-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(381) 1-(3-phenylpropyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(382) 1-(2-hydroxyethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(383) 1-(2-methoxyethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(384) 1-[2-(dimethylamino)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(385) 1-[2-(2,4,6-trimethylphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(386) 1-[2-(2,4-dichlorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(387) 1-(2-thiophen-2-yl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(388) 1-(2-thiophen-3-yl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(389) 1-[2-(4-tert-butylphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(390) 1-[2-(2-fluorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(391) 1-[2-(2-methylphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(392) 1-[2-(3-methylphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(393) 1-[2-(1-naphthyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(394) 1-[2-(2-naphthyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(395) 1-(4-phenylbutyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(396) 1-[2-(3-trifluoromethylphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-

[(2-aminocyclohexyl)amino]xanthine
(397) 1-[2-(pyridin-2-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(398) 1-[2-(pyrrol-1-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(399) 1-[2-([1,2,3]triazol-1-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(400) 1-[2-(pyridin-4-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(401) 1-(3-buten-1-yl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(402) 1-(4-pentin-1-yl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(403) 1-[2-(4-methylthiazol-5-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(404) 1-[2-(3-bromophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(405) 1-[2-(3-chlorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(406) 1-((E)-2-phenylvinyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(407) 1-[2-(2-chlorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(408) 1-[2-(2-trifluoromethylphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(409) 1-[2-(2-bromophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(410) 1-[2-(3-fluorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(411) 1-[2-(3-nitrophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(412) 1-[2-(4-methylphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(413) 1-[2-(4-hydroxyphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(414) 1-[2-(3-hydroxyphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(415) 1-[(methoxycarbonyl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(416) 1-[2-(methoxycarbonyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(417) 1-phenyl-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(418) 1-[2-(3,5-difluorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(419) 1-[2-(2,6-difluorophenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(420) 1-[2-(thiophen-3-yl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(421) 1-[2-(3-cyanomethoxyphenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(422) 1-[2-(3-benzyloxyphenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(423) 1-[2-(3-phenylsulfonyloxyphenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(424) 1-[2-(3-hydroxyphenyl)-2-oxoethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(425) 1-[2-(3,5-dimethoxyphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(426) 1-[3-(methoxycarbonyl)propyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(427) 1-{2-[4-(ethoxycarbonyl)phenyl]ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(428) 1-(phenylsulfanylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(429) 1-(phenylsulfinylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(430) 1-(2-methoxycarbonyl-2-propen-1-yl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(431) 1-[(pyridin-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(432) 1-[2-(3-phenyloxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(433) 1-[2-(3-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(434) 1-(2-{3-[bis(methanesulfonyl)-amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(435) 1-[2-(2-bromo-5-dimethylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(436) 1-[2-(3-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(437) 1-[2-(3-methoxycarbonylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(438) 1-[2-(3-acetylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(439) 1-[2-(3-{[(ethoxycarbonylamino)carbonyl]amino}-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(440) 1-[2-(3-cyanomethylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(441) 1-[(thiazol-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(442) 1-[(isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(443) 1-[(isoquinolin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(444) 1-[(benzo[d]isoisthiazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(445) 1-[(benzo[d]isoxazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(446) 1-[(pyridin-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(447) 1-[(pyridin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(448) 1-[(isoxazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(449) 1-[(1-naphthyl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(450) 1-[(aminocarbonyl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(451) 1-[2-(3-methanesulfonylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(452) 1-[2-(2-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(453) 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(454) 1-[2-{3-[(methylamino)thiocarbonylamino]-phenyl}-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(455) 1-[2-(2-acetylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(456) 1-[6-methyl-piridin-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(457) 1-[(1-methyl-1H-indazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(458) 1-(2-{3-[(methoxycarobnyl)methylamino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(459) 1-cyanomethyl-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(460) 1-[2-(2-hydroxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(461) 1-[2-(2-methanesulfonyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(462) 1-[2-{2-[(methoxycarobnyl)methoxy]-phenyl}-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(463) 1-[2-(2-cyanomethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(464) 1-(2-{3-[(methylaminocarbonyl)methoxy]-phenyl}-2-oxo-ethyl)-3-methyl-7-

(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(465) 1-(2-{3-[(aminocarbonyl)methoxy]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(466) 1-(2-{3-[(dimethylaminocarbonyl)amino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(467) 1-(4-oxo-4H-chromen-3-yl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(468) 1-[(3-methyl-pyridin-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(469) 1-[(5-methyl-pyridin-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(470) 1-[(4-methyl-pyridin-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(471) 1-[(quinoline-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(472) 1-[(quinoline-8-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(473) 1-[(5-nitro-isoquinoline-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(474) 1-[(2-oxo-1,2-dihydro-quinoline-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(475) 1-[(5-amino-isoquinoline-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(476) 1-[2-(3-aminosulfonyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(477) 1-(2-phenoxy-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-

aminocyclohexyl)amino]xanthine
(478) 1-carboxymethyl-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(479) 1-(3-carboxy-propyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(480) 1-[2-(4-carboxy-phenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(481) 1-(2-phenyl-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(482) 1-[2-(3-amino-phenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(483) 1-[2-(pyrrolidin-1-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(484) 1-[2-(piperidin-1-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(485) 1-[2-(morpholin-4-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(486) 1-[2-(piperazin-1-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(487) 1-[2-(4-methyl-piperazin-1-yl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(488) 1-(3-hydroxypropyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(489) 1-(3-methoxypropyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(490) 1-(3-ethoxypropyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(491) 1-[3-(dimethylamino)propyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(492) 1-[3-(pyrrolidin-1-yl)propyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(493) 1-[3-(morpholin-4-yl)propyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(494) 1-[3-(piperazin-1-yl)propyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(495) 1-[3-(4-methyl-piperazin-1-yl)propyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(496) 1-(pyrrolidin-1-yl-carbonylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(497) 1-(piperidin-1-yl-carbonylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(498) 1-(morpholin-4-yl-carbonylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(499) 1-[2-(3-fluoro-4-hydroxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(500) 1-[2-(4-methoxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(501) 1-[2-(4-ethoxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(502) 1-(2-{4-[(carboxymethyl)oxy]-phenyl}-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(503) 1-[2-(2-fluoro-5-hydroxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(504) 1-[2-(3-methoxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(505) 1-{2-[3-(carboxymethyloxy)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(506) 1-(2-{3-[(ethoxycarbonyl)methyloxy]-phenyl}-ethyl)-3-methyl-7-(2-methyl-

5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(507) 1-[2-(2-hydroxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(508) 1-[2-(2-methoxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(509) 1-{2-[2-(carboxymethyloxy)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(510) 1-(2-{2-[(methoxycarbonyl)methyloxy]-phenyl}-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(511) 1-[2-(4-hydroxymethyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(512) 1-{2-[4-(methoxycarbonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(513) 1-{2-[4-(carboxymethyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(514) 1-(2-{4-[(methoxycarbonyl)methyl]-phenyl}-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(515) 1-{2-[4-(2-carboxy-ethyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(516) 1-(2-{4-[2-(methoxycarbonyl)-ethyl]-phenyl}-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(517) 1-[2-(3-methyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(518) 1-[2-(3-carboxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(519) 1-{2-[3-(ethoxycarbonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-

fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(520) 1-{2-[3-(carboxymethyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(521) 1-(2-{3-[(methoxycarbonyl)methyl]-phenyl}-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(522) 1-{2-[3-(2-carboxy-ethyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(523) 1-(2-{3-[2-(methoxycarbonyl)-ethyl]-phenyl}-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(524) 1-[2-(2-methyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(525) 1-[2-(2-carboxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(526) 1-{2-[2-(methoxycarbonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(527) 1-[2-(4-fluoro-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(528) 1-[2-(4-chloro-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(529) 1-[2-(4-bromo-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(530) 1-[2-(4-cyano-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(531) 1-[2-(4-trifluoromethoxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(532) 1-[2-(4-methylsulfanyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(533) 1-[2-(4-methylsulfinyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-

8-[(2-aminocyclohexyl)amino]xanthine
(534) 1-[2-(4-methylsulfonyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(535) 1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(536) 1-[2-(4-amino-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(537) 1-(2-{4-[(methylcarbonyl)amino]-phenyl}-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(538) 1-(2-{4-[(methylsulfonyl)amino]-phenyl}-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(539) 1-{2-[4-(aminocarbonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(540) 1-{2-[4-(methylaminocarbonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(541) 1-{2-[4-(dimethylaminocarbonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(542) 1-{2-[4-(aminosulfonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(543) 1-{2-[4-(methylaminosulfonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(544) 1-{2-[4-(dimethylaminosulfonyl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(545) 1-[3-(ethoxycarbonyl)-propyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(546) 1-[2-(3,4-dimethyl-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(547) 1-[2-(2-fluoro-5-chloro-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(548) 1-[2-(3,5-dimethoxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(549) 1-[2-(naphthalene-2-yl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(550) 1-[2-(pyridin-3-yl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(551) 1-[4-phenyl-butyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(552) 1-(2-phenylsulfanyl-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(553) 1-(2-phenylsulfinyl-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(554) 1-(2-phenylsulfonyl-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(555) 1-[2-(3-fluoro-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(556) 1-[2-(3-chloro-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(557) 1-[2-(3-bromo-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(558) 1-[2-(3-methyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(559) 1-[2-(3-trifluoromethyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(560) 1-[2-(2-methyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(561) 1-[2-(3-difluoromethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(562) 1-[2-(3-trifluoromethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-

fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(563) 1-[2-(3-ethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(564) 1-[2-(3-isopropyloxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(565) 1-[2-(3-cyclopropyloxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(566) 1-[2-(3-cyclopentyloxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(567) 1-[2-(3-cyclopropylmethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(568) 1-{2-[3-(2,2,2-trifluoroethoxy)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(569) 1-[2-(4-hydroxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(570) 1-{2-[3-(methylcarbonylamino)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(571) 1-{2-[3-(aminocarbonylamino)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(572) 1-{2-[3-(methylaminocarbonylamino)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(573) 1-{2-[3-(dimethylaminocarbonylamino)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(574) 1-{2-[3-(methylsulfonylamino)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(575) 1-{2-[3-(aminosulfonyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(576) 1-{2-[3-(methylaminosulfonyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(577) 1-{2-[3-(dimethylaminosulfonyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(578) 1-[2-(3-ethynyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(579) 1-[2-(3-cyano-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(580) 1-{2-[3-(aminocarbonyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(581) 1-{2-[3-(methylaminocarbonyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(582) 1-{2-[3-(dimethylaminocarbonyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(583) 1-{2-[3-(methylsulfanyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(584) 1-{2-[3-(methylsulfinyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(585) 1-{2-[3-(methylsulfonyl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(586) 1-[2-(3,5-dimethyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(587) 1-[2-(3-fluoro-5-methyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(588) 1-[2-(pyridin-3-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(589) 1-[2-(furan-2-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(590) 1-[2-(thiophen-2-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(591) 1-[2-(thiazole-2-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(592) 1-[2-(thiazole-5-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(593) 1-[2-(thiazole-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(594) 1-(2-phenyl-2-hydroxyimino-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(595) 1-(2-phenyl-2-methoxyimino-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(596) 1-(2-oxo-propyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(597) 1-(2-oxo-butyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-

aminocyclohexyl)amino]xanthine
(598) 1-(3-methyl-2-oxo-butyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(599) 1-(2-cyclopropyl-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(600) 1-(2-cyclohexyl-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(601) 1-(3-dimethylamino-2,3-dioxo-propyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(602) 1-[3-(piperidin-1-yl)-2,3-dioxo-propyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(603) 1-(2-phenyl-2-hydroxy-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(604) 1-(2-phenyl-2-hydroxy-propyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(605) 1-(2-phenyl-2-methoxy-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(606) 1-[(quinazolyn-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(607) 1-[(5-methyl-isoxazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(608) 1-[(oxazol-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(609) 1-[(1H-indazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(610) 1-[(5-fluoro-benzo[d]isothiazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(611) 1-[(5-fluoro-benzo[d]isoxazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(612) 1-[(5-methyl-benzo[d]isoxazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(613) 1-[(5-methyl-benzo[d]isothiazol-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(614) 1-(2-cyclohexyl-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(615) 1-[2-(2-difluoromethoxy-phenyl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(616) 1-[2-(2-difluoromethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(617) 1-[2-(2-trifluoromethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(618) 1-[2-(indan-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(619) 1-[2-(benzo[1,3]dioxol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(620) 1-[2-(2,2-difluoro-benzo[1,3]dioxol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(621) 1-[2-(naphtho-1-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(622) 1-[2-(2-isopropyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(623) 1-[2-(2-cyclopropyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(624) 1-[2-(2-cyclopentyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(625) 1-[2-(2-phenyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-

[(2-aminocyclohexyl)amino]xanthine
(626) 1-[2-(2-cyclopentylmethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(627) 1-(3-phenyl-2-oxo-propyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(628) 1-(3-phenyl-3-oxo-propyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(629) 1-[2-(2-methylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(630) 1-{2-[2-(N-cyanomethyl-N-methyl-amino)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(631) 1-[2-(2-cyanomethylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(632) 1-(2-{2-[(methoxycarbonyl)methylamino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(633) 1-[2-(2-methylsulfonylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(634) 1-[2-(3-methylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(635) 1-{2-[3-(N-cyanomethyl-N-methyl-amino)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(636) 1-(2-{3-[(dimethylamino)sufonylamino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(637) 1-(2-{3-[(morpholin-4-yl)sulfonylamino]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(638) 1-[2-(3-aminosulfonylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(639) 1-[2-(3-ethylsulfonylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(640) 1-[2-(3-isopropylsulfonylamino-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(641) 1-{2-[3-(2-oxo-imidazolin-1-yl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(642) 1-{2-[3-(3-methyl-2-oxo-imidazolidine-1-yl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(643) 1-{2-[3-(3-methyl-2,5-dioxo-imidazolidine-1-yl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(644) 1-{2-[3-(3-methyl-2,4-dioxo-imidazolidine-1-yl)-phenyl]-2-oxo-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(645) 1-[(1-methyl-2-oxo-1,2-dihydro-quinolin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(646) 1-[(2-oxo-1,2-dihydro-quinazolin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(647) 1-[(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(648) 1-[(2-cyano-naphthalen-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(649) 1-[(6-cyano-naphthalen-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(650) 1-[(5-cyano-naphthalen-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(651) 1-[(8-methyl-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(652) 1-[(5-cyano-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(653) 1-[(5-aminocarbonyl-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(654) 1-[(5-aminosulfonyl-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(655) 1-[(5-methylsulfonyl-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(656) 1-[(5-methylsulfonylamino-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(657) 1-[(5-methoxy-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(658) 1-[(6-methoxy-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(659) 1-[(7-methylsulfonylamino-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(660) 1-[(7-cyano-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(661) 1-[(7-aminocarbonyl-isoquinolin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(662) 1-[2-(2-aryloxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(663) 1-[2-(3-{[(morpholin-4-yl)carbonyl]methoxy}-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(664) 1-[2-(3-carboxymethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(665) 1-[2-(3-methylsulfanylmethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(666) 1-[2-(3-methylsulfinylmethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(667) 1-[2-(3-methylsulfonylmethoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(668) 1-[2-(2-oxo-2,3-dihydro-benzoxazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(669) 1-[2-(2-oxo-2,3-dihydro-1H-benzoimidazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(670) 1-[2-(1-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(671) 1-[2-(1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzoimidazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(672) 1-[2-(1H-benzoimidazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(673) 1-[2-(2-methyl-1H-benzoimidazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(674) 1-[2-(benzoxazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(675) 1-[2-(2-methyl-benzoxazol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(676) 1-[2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-5-yl-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(677) 1-[2-(benzo[1,3]dioxol-4-yl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(678) 1-(1-methoxycarbonyl-1-phenyl-methyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(679) 1-(1-carboxy-1-phenyl-methyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(680) 1-(1-aminocarbonyl-1-phenyl-methyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(681) 1-(1-methoxycarbonyl-2-phenyl-methyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(682) 1-(1-carbonyl-2-phenyl-methyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(683) 1-(1-aminocarbonyl-2-phenyl-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-

8-[(2-aminocyclohexyl)amino]xanthine

(684) 1-[(benzofuran-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(685) 1-[(2,3-dihydro-benzofuran-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(686) 1-[2-(2-amino-3-cyano-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(687) 1-[2-(2-amino-3-fluoro-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(688) 1-(1-methyl-2-phenyl-2-oxo-ethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(689) 1-[2-oxo-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(690) 1-[2-oxo-2-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(691) 1-[(2-oxo-2H-chromen-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(692) 1-[(1-oxo-1,2-dihydro-isoquinolin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(693) 1-[(2-methyl-1-oxo-1,2-dihydro-isoquinolin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(694) 1-[(4-oxo-3,4-dihydro-phthalazin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(695) 1-[(3-methyl-4-oxo-3,4-dihydro-phthalazin-1-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(696) 1-[([1,5]naphthylidin-4-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(697) 1-[([1,7]naphthylidin-8-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(698) 1-[(quinolin-2-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(699) 1-[(isoquinolin-3-yl)methyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(700) 1-{2-oxo-2-[3-(2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(701) 1-{2-oxo-2-[3-(3-methyl-2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-ethyl}-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(702) 1-(2-phenyl-2-oxoethyl)-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(703) 1-(2-phenyl-2-oxoethyl)-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(704) 1-[(isoquinolin-1-yl)methyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(705) 1-[(isoquinolin-1-yl)methyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(706) 1-[2-(pyridin-2-yl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(707) 1-[2-(pyridin-2-yl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(708) 1-[2-(2-naphthyl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(709) 1-[2-(2-naphthyl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-

aminocyclohexyl)amino]xanthine
(710) 1-[2-(2-methoxyphenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(711) 1-[2-(2-methoxyphenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(712) 1-[2-(3-methoxyphenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(713) 1-[2-(3-methoxyphenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(714) 1-[2-(2-chlorophenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(715) 1-[2-(2-chlorophenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(716) 1-[2-(3-chlorophenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(717) 1-[2-(3-chlorophenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(718) 1-(2-phenylethyl)-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(719) 1-(2-phenylethyl)-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(720) 3-methyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(721) 3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(722) 3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(723) 1-[2-(phenyl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(724) 1-[(pyridin-2-yl)methyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(725) 1-[2-(2-fluorophenyl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(726) 1-[2-(2-chlorophenyl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(727) 1-[2-(2-bromophenyl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(728) 1-[2-(2-cyanophenyl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(729) 1-[2-(2-methoxyphenyl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(730) 1-[2-(2-methylphenyl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(731) 1-[2-(3-fluorophenyl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(732) 1-[2-(3-chlorophenyl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(733) 1-[2-(3-bromophenyl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(734) 1-[2-(3-cyanophenyl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(735) 1-[2-(3-methoxyphenyl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(736) 1-[2-(3-methylphenyl)ethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(737) 1-[2-(phenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(738) 1-[2-(2-fluorophenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-

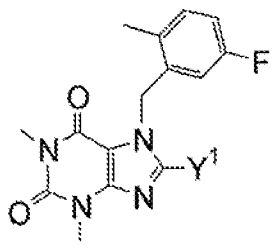
[(2-aminocyclohexyl)amino]xanthine
(739) 1-[2-(2-bromophenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(740) 1-[2-(2-cyanophenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(741) 1-[2-(2-methylphenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(742) 1-[2-(3-fluorophenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(743) 1-[2-(3-bromophenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(744) 1-[2-(3-cyanophenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(745) 1-[2-(3-methylphenyl)-2-oxoethyl]-3-methyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(746) 1-[2-(phenyl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(747) 1-[(pyridin-2-yl)methyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(748) 1-[2-(2-fluorophenyl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(749) 1-[2-(2-chlorophenyl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(750) 1-[2-(2-bromophenyl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(751) 1-[2-(2-cyanophenyl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(752) 1-[2-(2-methoxyphenyl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-

aminocyclohexyl)amino]xanthine
(753) 1-[2-(2-methylphenyl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(754) 1-[2-(3-fluorophenyl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(755) 1-[2-(3-chlorophenyl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(756) 1-[2-(3-bromophenyl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(757) 1-[2-(3-cyanophenyl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(758) 1-[2-(3-methoxyphenyl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(759) 1-[2-(3-methylphenyl)ethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(760) 1-[2-(phenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(761) 1-[2-(2-fluorophenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(762) 1-[2-(2-bromophenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(763) 1-[2-(2-cyanophenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(764) 1-[2-(2-methylphenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(765) 1-[2-(3-fluorophenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(766) 1-[2-(3-bromophenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine

(767) 1-[2-(3-cyanophenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(768) 1-[2-(3-methylphenyl)-2-oxoethyl]-3-methyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclohexyl)amino]xanthine
(769) 1,3-dimethyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocycloheptyl)amino]xanthine
(770) 1,3-dimethyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocycloheptyl)amino]xanthine
(771) 1,3-dimethyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocycloheptyl)amino]xanthine
(772) 1,3-dimethyl-7-(2-methyl-5-fluorobenzyl)-8-[(2-aminocyclopentyl)amino]xanthine
(773) 1,3-dimethyl-7-(2-chloro-5-fluorobenzyl)-8-[(2-aminocyclopentyl)amino]xanthine
(774) 1,3-dimethyl-7-(2-bromo-5-fluorobenzyl)-8-[(2-aminocyclopentyl)amino]xanthine

Table 1



| Compound No. | $Y^1$ | Compound No. | $Y^1$ | Compound No. | $Y^1$ |
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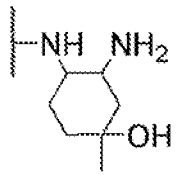
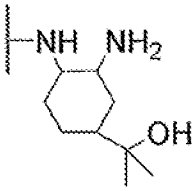
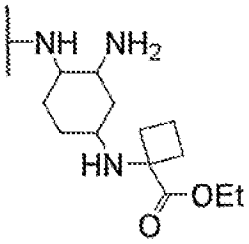
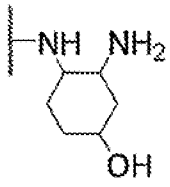
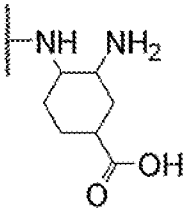
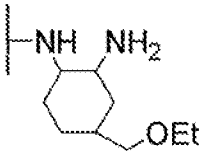
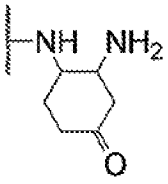
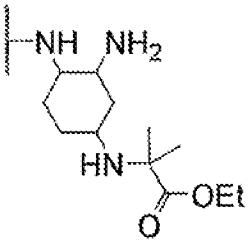
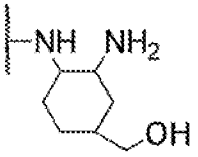
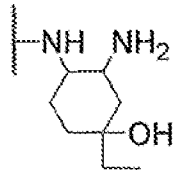
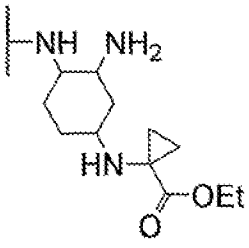
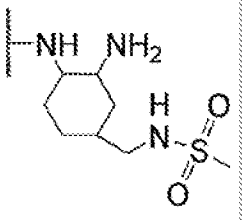
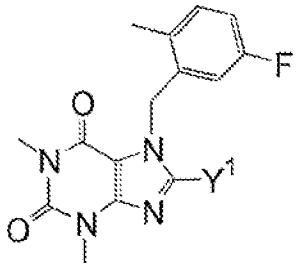
| 775 |  | 779 |  | 783 |  |
| 776 |  | 780 |  | 784 |  |
| 777 |  | 781 |  | 785 |  |
| 778 |  | 782 |  | 786 |  |

Table 2



| Compound No. | $Y^1$ | Compound No. | $Y^1$ | Compound No. | $Y^1$ |
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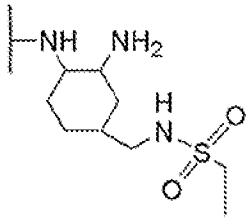
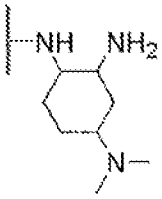
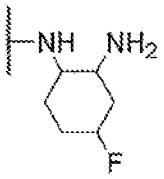
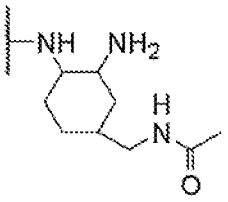
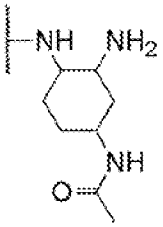
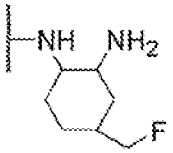
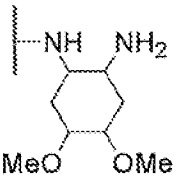
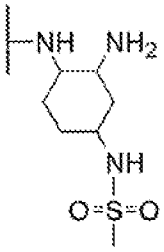
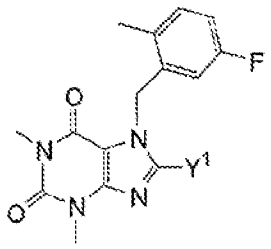
| 787 |  | 790 |  | 793 |  |
| 788 |  | 791 |  | 794 |  |
| 789 |  | 792 |  | | |

Table 3



| Compound No. | $Y^1$ | Compound No. | $Y^1$ | Compound No. | $Y^1$ |
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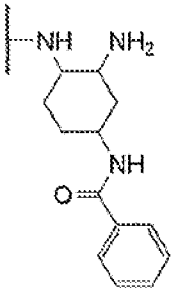
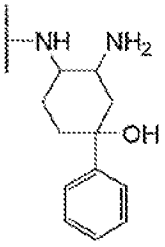
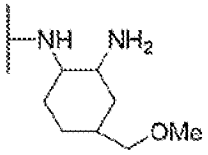
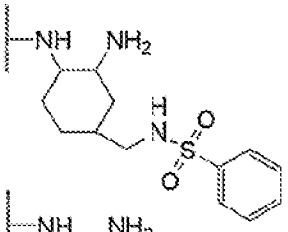
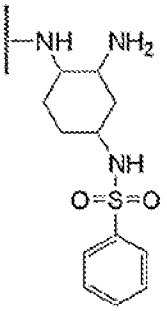
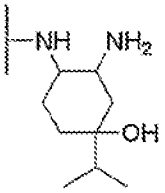
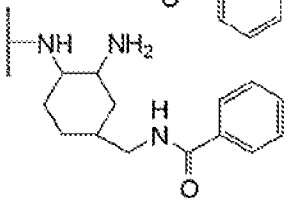
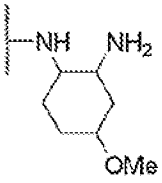
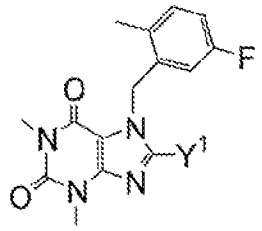
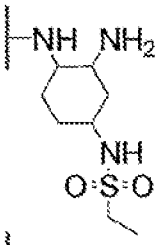
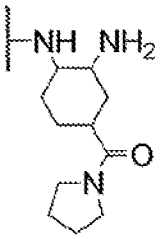
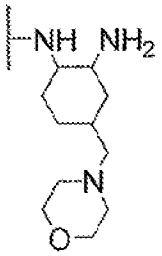
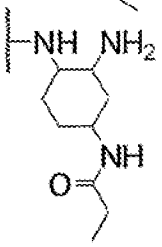
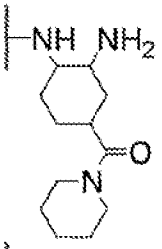
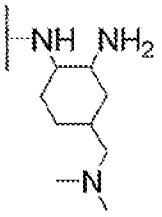
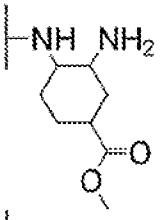
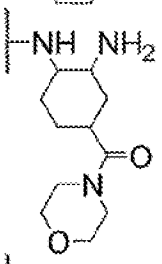
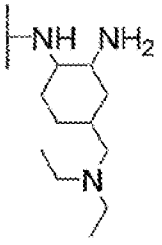
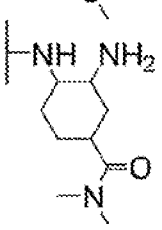
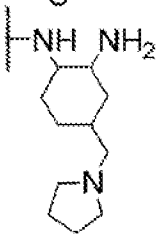
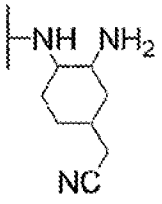
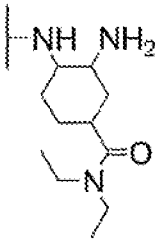
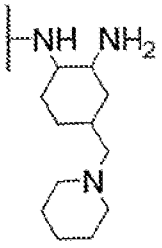
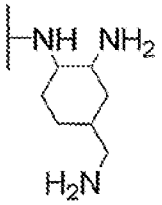
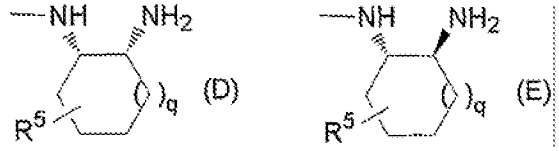
| 795 |  | 797 |  | 800 |  |
| | | | | 801 |  |
| 796 |  | 798 |  | 802 |  |
| | | 799 |  | | |

Table 4



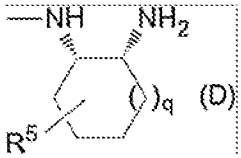
| Compound No. | $Y^1$ | Compound No. | $Y^1$ | Compound No. | $Y^1$ |
|---|---|---|---|---|---|
| 803 |  | 808 |  | 813 |  |
| 804 |  | 809 |  | 814 |  |
| 805 |  | 810 |  | 815 |  |
| 806 |  | 811 |  | 816 |  |
| 807 |  | 812 |  | 817 |  |

Preferably, compound Nos. 352 to 817 above have a cycloalkanediamine compound with a diamino group having the absolute configuration represented by formula (D) or formula (E) below.



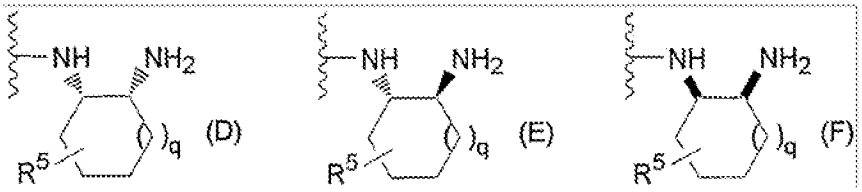
(In the formulae, q and $R^5$ are the same as above.)

More preferably, compound Nos. 352 to 817 above have a cycloalkanediamine compound with a diamino group having the absolute configuration represented by formula (D) below.



(In the formula, q and $R^5$ are the same as above.)

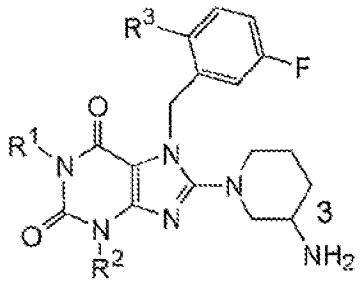
Additionally, in the description below, the absolute configuration of the amino group is represented when the bonds are depicted by the solid-line and broken-line wedge forms as in formula (D) and formula (E); and the relative configuration of the amino group is represented when the bonds are depicted by bold lines as in formula (F) (formula (F), for example, represents a (±)-cis unit).



(In the formulae, q and $R^5$ are the same as above.)

Moreover, the 3-aminopiperidine compound below is also a preferable example of the xanthine compound of the present invention.

Table 5



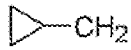
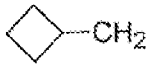
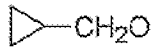
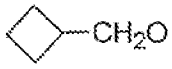
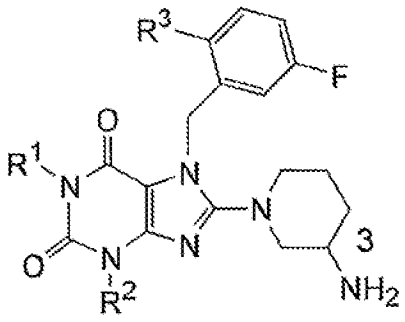
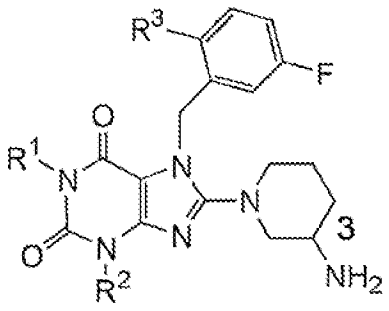
| No. | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| 818 | $CH_3$ | $CH_3$ | $CHF_2O$ |
| 819 | $CH_3$ | $CH_3$ | $CF_3CF_2O$ |
| 820 | $CH_3$ | $CH_3$ | $CF_3O$ |
| 821 | $CH_3$ | $CH_3$ | $C_2H_5$ |
| 822 | $CH_3$ | $CH_3$ | CN |
| 823 | $CH_3$ | $CH_3$ | $CH_3(CH_2)_2$ |
| 824 | $CH_3$ | $CH_3$ | $(CH_3)_2CH$ |
| 825 | $CH_3$ | $CH_3$ |  |
| 826 | $CH_3$ | $CH_3$ |  |
| 827 | $CH_3$ | $CH_3$ | $CH_3(CH_2)_2O$ |
| 828 | $CH_3$ | $CH_3$ | $(CH_3)_2CHO$ |
| 829 | $CH_3$ | $CH_3$ |  |
| 830 | $CH_3$ | $CH_3$ |  |
| 831 | $CH_3$ | $CH_3$ | $CH_3S(O)_2$ |
| 832 | $CH_3$ | $CH_3$ | $CH_3S(O)$ |
| 833 | $CH_3$ | $CH_3$ | $CH_3S$ |
| 834 | $CH_3$ | $CH_3$ | $CO_2H$ |
| 835 | $CH_3$ | $CH_3$ | $CONH_2$ |
| 836 | $CH_3$ | $CH_3$ | $CONHCH_3$ |
| 837 | $CH_3$ | $CH_3$ | $CON(CH_3)_2$ |
| 838 | $CH_3$ | $CH_3$ | I |
| 839 | $CH_3$ | $CH_3$ | F |
| 840 | $CH_3$ | $CH_3$ | $NH_2$ |
| 841 | $CH_3$ | $CH_3$ | $NHCH_3$ |
| 842 | $CH_3$ | $CH_3$ | $N(CH_3)_2$ |
| 843 | $CH_3$ | $CH_3$ | Cl |
| 844 | $CH_3$ | $CH_3$ | $CH_3O$ |

Table 6



| No. | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| 845 | H | $CH_3$ | $CHF_2O$ |
| 846 | H | $CH_3$ | $CF_3CF_2O$ |
| 847 | H | $CH_3$ | $CF_3O$ |
| 848 | H | $CH_3$ | $C_2H_5$ |
| 849 | H | $CH_3$ | CN |
| 850 | H | $CH_3$ | $CH_3(CH_2)_2$ |
| 851 | H | $CH_3$ | $(CH_3)_2CH$ |
| 852 | H | $CH_3$ | $CH_3O$ |
| 853 | H | $CH_3$ | Cl |
| 854 | H | $C_2H_5$ | $CHF_2O$ |
| 855 | H | $C_2H_5$ | $CF_3CF_2O$ |
| 856 | H | $C_2H_5$ | $CF_3O$ |
| 857 | H | $C_2H_5$ | $C_2H_5$ |
| 858 | H | $C_2H_5$ | CN |
| 859 | H | $C_2H_5$ | $CH_3(CH_2)_2$ |
| 860 | H | $C_2H_5$ | $(CH_3)_2CH$ |
| 861 | H | $C_2H_5$ | $CH_3O$ |
| 862 | H | $C_2H_5$ | Cl |
| 863 | $CH_3$ | $CH_3$ | $CH_3C(O)$ |
| 864 | $CH_3$ | $CH_3$ | $C_2H_5C(O)$ |

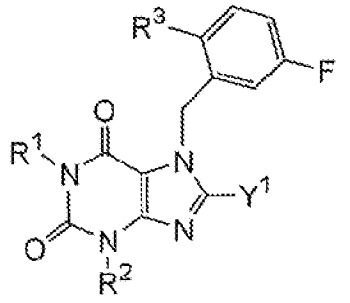
Table 7



| No. | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| 865 | $CH_3$ | $CH_3$ | $CH_2$=CH |
| 866 | $CH_3$ | $CH_3$ | (E)-$CH_3$CH=CH |
| 867 | $CH_3$ | $CH_3$ | (Z)-$CH_3$CH=CH |
| 868 | $CH_3$ | $CH_3$ | $CH_2$=CH$CH_2$ |
| 869 | $CH_3$ | $CH_3$ | HO$CH_2CH_2$ |
| 870 | $CH_3$ | $CH_3$ | NC$CH_2CH_2$ |
| 871 | $CH_3$ | $CH_3$ | HOC(O)$CH_2$ |
| 872 | $CH_3$ | $CH_3$ | $H_2$NC(O)CH2 |
| 873 | $CH_3$ | $CH_3$ | $CH_3$C≡C |

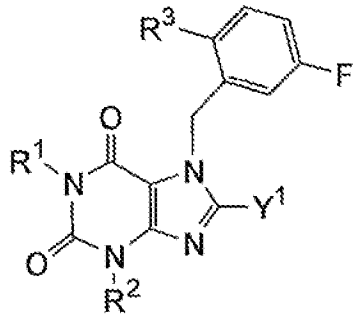
In compounds Nos. 818 to 873 above, compounds with an R- configuration in position 3 of the 3-aminopiperidine are preferable.

Table 8



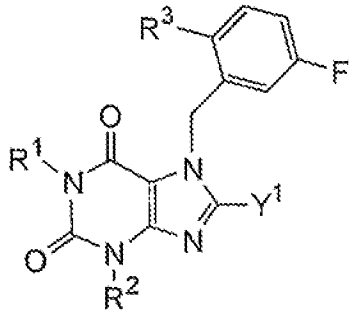
| No. | $R^1$ | $R^2$ | $R^3$ | $Y^1$ |
|---|---|---|---|---|
| 874 | $CH_3$ | $CH_3$ | Cl | D1 |
| 875 | $CH_3$ | $CH_3$ | Cl | D2 |
| 876 | $CH_3$ | $CH_3$ | Br | D3 |
| 877 | $CH_3$ | $CH_3$ | $CH_3$ | D4 |
| 878 | $CH_3$ | $CH_3$ | Cl | D5 |
| 879 | $CH_3$ | $CH_3$ | Br | D6 |
| 880 | $CH_3$ | $CH_3$ | $CH_3$ | D7 |
| 881 | $CH_3$ | $CH_3$ | Cl | D8 |
| 882 | $CH_3$ | $CH_3$ | Br | D9 |
| 883 | $CH_3$ | $CH_3$ | $CH_3$ | D10 |
| 884 | $CH_3$ | $CH_3$ | Cl | D11 |
| 885 | $CH_3$ | $CH_3$ | Br | D12 |
| 886 | $CH_3$ | $CH_3$ | $CH_3$ | D13 |
| 887 | $CH_3$ | $CH_3$ | Cl | D14 |
| 888 | $CH_3$ | $CH_3$ | Br | D15 |
| 889 | $CH_3$ | $CH_3$ | $CH_3$ | D16 |
| 890 | $CH_3$ | $CH_3$ | Cl | D17 |
| 891 | $CH_3$ | $CH_3$ | Br | D18 |
| 892 | $CH_3$ | $CH_3$ | $CH_3$ | D19 |
| 893 | $CH_3$ | $CH_3$ | Cl | D20 |
| 894 | $CH_3$ | $CH_3$ | Br | D21 |
| 895 | $CH_3$ | $CH_3$ | $CH_3$ | D22 |
| 896 | $CH_3$ | $CH_3$ | Cl | D23 |
| 897 | $CH_3$ | $CH_3$ | Br | D24 |
| 898 | $CH_3$ | $CH_3$ | Cl | D25 |
| 899 | $CH_3$ | $CH_3$ | Br | D26 |

Table 9



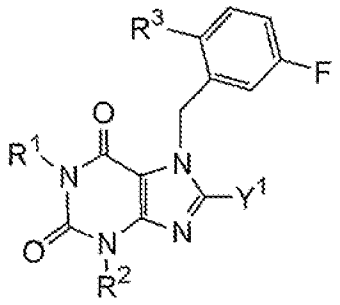
| No. | $R^1$ | $R^2$ | $R^3$ | $Y^1$ |
|---|---|---|---|---|
| 900 | $CH_3$ | $CH_3$ | $CH_3$ | D27 |
| 901 | $CH_3$ | $CH_3$ | Cl | D28 |
| 902 | $CH_3$ | $CH_3$ | Br | D29 |
| 903 | $CH_3$ | $CH_3$ | $CH_3$ | D30 |
| 904 | $CH_3$ | $CH_3$ | Cl | D31 |
| 905 | $CH_3$ | $CH_3$ | Br | D32 |
| 906 | $CH_3$ | $CH_3$ | $CH_3$ | D1 |
| 907 | $CH_3$ | $CH_3$ | Br | D1 |
| 908 | $CH_3$ | $CH_3$ | $CH_3$ | D2 |
| 909 | $CH_3$ | $CH_3$ | Br | D2 |
| 910 | $CH_3$ | $CH_3$ | Br | D5 |
| 911 | $CH_3$ | $CH_3$ | $CH_3$ | D5 |
| 912 | $CH_3$ | $CH_3$ | $CH_3$ | D14 |
| 913 | $CH_3$ | $CH_3$ | Br | D14 |
| 914 | $CH_3$ | $CH_3$ | $CH_3$ | D17 |
| 915 | $CH_3$ | $CH_3$ | Br | D17 |
| 916 | $CH_3$ | $CH_3$ | Cl | D18 |
| 917 | $CH_3$ | $CH_3$ | $CH_3$ | D18 |

Table 10



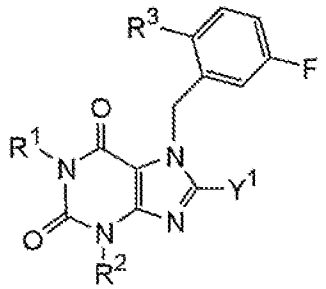
| No. | $R^1$ | $R^2$ | $R^3$ | $Y^1$ |
|---|---|---|---|---|
| 918 | H | $CH_3$ | Cl | D1 |
| 919 | H | $CH_3$ | Br | D1 |
| 920 | H | $CH_3$ | $CH_3$ | D1 |
| 921 | H | $CH_3$ | Br | D2 |
| 922 | H | $CH_3$ | $CH_3$ | D2 |
| 923 | H | $CH_3$ | Cl | D2 |
| 924 | H | $CH_3$ | Br | D5 |
| 925 | H | $CH_3$ | Cl | D5 |
| 926 | H | $CH_3$ | $CH_3$ | D5 |
| 927 | H | $CH_3$ | Cl | D14 |
| 928 | H | $CH_3$ | $CH_3$ | D14 |
| 929 | H | $CH_3$ | Br | D14 |
| 930 | H | $CH_3$ | Br | D17 |
| 931 | H | $CH_3$ | $CH_3$ | D17 |
| 932 | H | $CH_3$ | Cl | D17 |
| 933 | H | $CH_3$ | Br | D18 |
| 934 | H | $CH_3$ | Cl | D18 |
| 935 | H | $CH_3$ | $CH_3$ | D18 |

Table 11



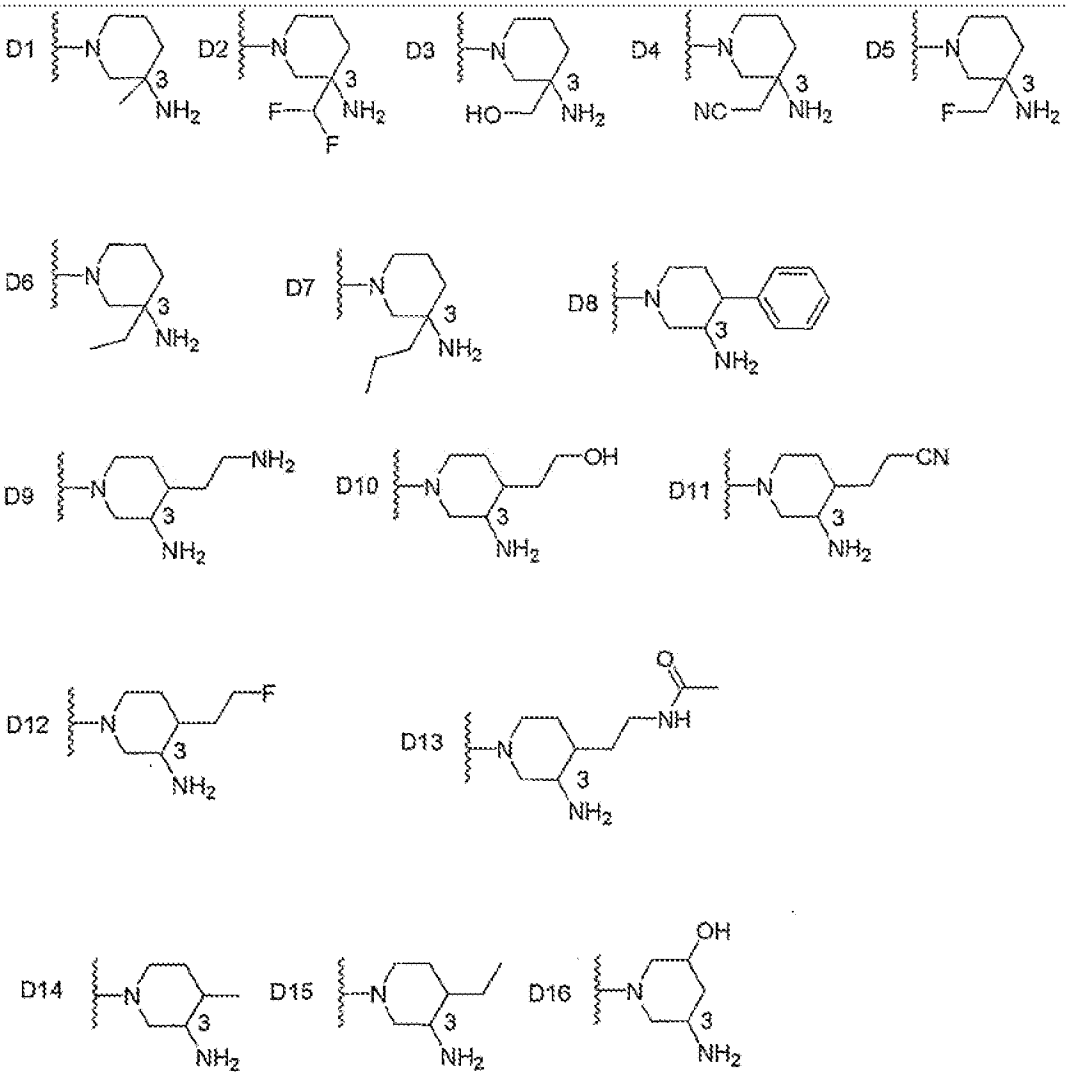
| No. | $R^1$ | $R^2$ | $R^3$ | $Y^1$ |
|---|---|---|---|---|
| 936 | $C_2H_5$ | $CH_3$ | Cl | D1 |
| 937 | $C_2H_5$ | $CH_3$ | Br | D1 |
| 938 | $C_2H_5$ | $CH_3$ | $CH_3$ | D1 |
| 939 | $C_2H_5$ | $CH_3$ | Br | D2 |
| 940 | $C_2H_5$ | $CH_3$ | $CH_3$ | D2 |
| 941 | $C_2H_5$ | $CH_3$ | Cl | D2 |
| 942 | $C_2H_5$ | $CH_3$ | Br | D5 |
| 943 | $C_2H_5$ | $CH_3$ | Cl | D5 |
| 944 | $C_2H_5$ | $CH_3$ | $CH_3$ | D5 |
| 945 | $C_2H_5$ | $CH_3$ | Cl | D14 |
| 946 | $C_2H_5$ | $CH_3$ | $CH_3$ | D14 |
| 947 | $C_2H_5$ | $CH_3$ | Br | D14 |
| 948 | $C_2H_5$ | $CH_3$ | Br | D17 |
| 949 | $C_2H_5$ | $CH_3$ | $CH_3$ | D17 |
| 950 | $C_2H_5$ | $CH_3$ | Cl | D17 |
| 951 | $C_2H_5$ | $CH_3$ | Br | D18 |
| 952 | $C_2H_5$ | $CH_3$ | Cl | D18 |
| 953 | $C_2H_5$ | $CH_3$ | $CH_3$ | D18 |

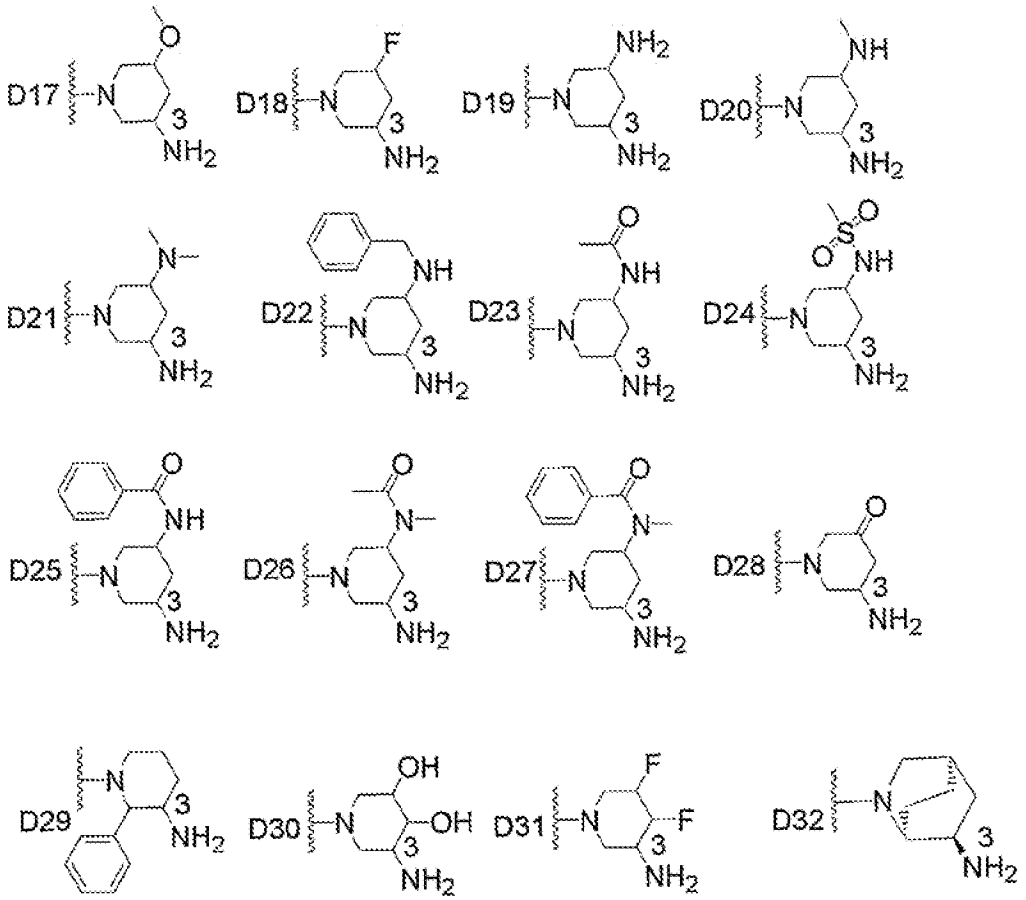
Table 12



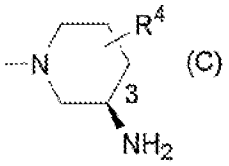
| No. | $R^1$ | $R^2$ | $R^3$ | $Y^1$ |
|---|---|---|---|---|
| 954 | $CH_3$ | H | Cl | D1 |
| 955 | $CH_3$ | H | Br | D1 |
| 956 | $CH_3$ | H | $CH_3$ | D1 |
| 957 | $CH_3$ | H | Br | D2 |
| 958 | $CH_3$ | H | $CH_3$ | D2 |
| 959 | $CH_3$ | H | Cl | D2 |
| 960 | $CH_3$ | H | Br | D5 |
| 961 | $CH_3$ | H | Cl | D5 |
| 962 | $CH_3$ | H | $CH_3$ | D5 |
| 963 | $CH_3$ | H | Cl | D14 |
| 964 | $CH_3$ | H | $CH_3$ | D14 |
| 965 | $CH_3$ | H | Br | D14 |
| 966 | $CH_3$ | H | Br | D17 |
| 967 | $CH_3$ | H | $CH_3$ | D17 |
| 968 | $CH_3$ | H | Cl | D17 |
| 969 | $CH_3$ | H | Br | D18 |
| 970 | $CH_3$ | H | Cl | D18 |
| 971 | $CH_3$ | H | $CH_3$ | D18 |

D1 to D32 mean the following substitution groups.




D17
D18
D19
D20
D21
D22
D23
D24
D25
D26
D27
D28
D29
D30
D31
D32

In D1 to D31, substitution groups having the same configuration of the 3-aminopiperidine amino group as represented in formula (C) below are more preferable. Specifically, substitution groups in which position 3 of D1 to D29 is an R- configuration, and position 3 of D30 and D31 is an S- configuration are more preferable.



(C)

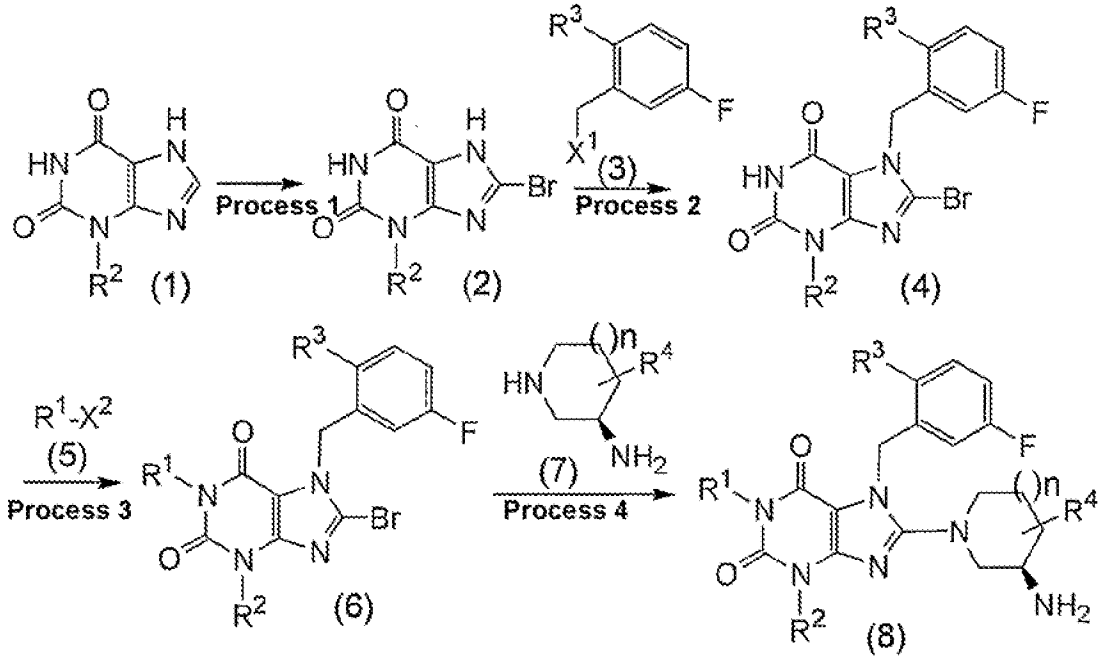
The production method of the compounds represented by formula (I) of the present invention will be explained below citing examples, but the present invention can in no way be limited to these. Further, the following abbreviation may be used in order to simplify the description.

Boc: tert-butoxycarbonyl group

The compound represented by formula (I) can be synthesized by combining well-known compounds using well-known methods of synthesis. For example, synthesis is possible using the following methods.

Production Method 1

Among the compounds represented by formula (1), the compound represented by formula (8) or a salt thereof can, for example, be produced by the method depicted below.



[In the formula, $R^1$, $R^2$, $R^3$, $R^4$, and n have the same meanings as those previously described. $X^1$ and $X^2$ represent an iodine atom, bromine atom, chlorine atom, methanesulfonyloxy, trifluoromethanesulfonyloxy, or p-toluenesulfonyloxy, and the like.]

1) Process 1

The compound (2) may be produced by allowing the compound (1) to react with bromine in an inactive solvent with or without the presence of additives (J. Heterocycl. Chem. 37, 1033 (2000), J. Chem. Soc., Perkin Trans. 1 13, 1833 (1999), J. Med. Chem. 38, 3838 (1995), etc.). Additives include sodium acetate and the like, and the amount added normally may be selected in the range of 1 to 5 weight equivalents to compound (1). The amount of bromine used may be selected in the range of 1 to 3 weight equivalents to compound (1). Water, alcohol (ethanol, methanol, isopropanol, and the like), ether (1,4-dioxane, and the like), organic acids (acetic acid, propionic acid, and the like), or mixtures of these may be cited as examples of inactive solvents. The reaction temperature may be selected in the range of approximately 20°C to approximately 50°C.

2) Process 2

The compound (4) may be produced by allowing the compound (2) to react with the compound (3) in an inactive solvent in the presence of a base (J. Heterocycl. Chem. 37, 1033 (2000), J. Chem. Soc., Perkin Trans. 1 13, 1833 (1999), J. Med. Chem. 38, 3838 (1995), etc.). The amount of the compound (3) used may be selected in the range of 1 to 3 weight equivalents to compound (2). Examples of the base include alkali carbonate (potassium carbonate, sodium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, and the like), alkali hydroxide (potassium hydroxide, sodium hydroxide, and the like), etc.; and potassium carbonate and the like is preferable. The amount of the base used may be selected in the range of 1 to 5 weight equivalents to compound (2). Examples of inactive solvents include non-protic solvents (dimethylformamide, dimethylsulfoxide, and the like) ether (diethylether, tetrahydrofuran, 1,4-dioxane, and the like), ketone (acetone, and the like), and mixtures of these, etc.; and dimethylformamide, dimethylsulfoxide, and the like are preferable. The reaction temperature may be selected in the range of approximately 10°C to approximately 50°C.

3) Process 3

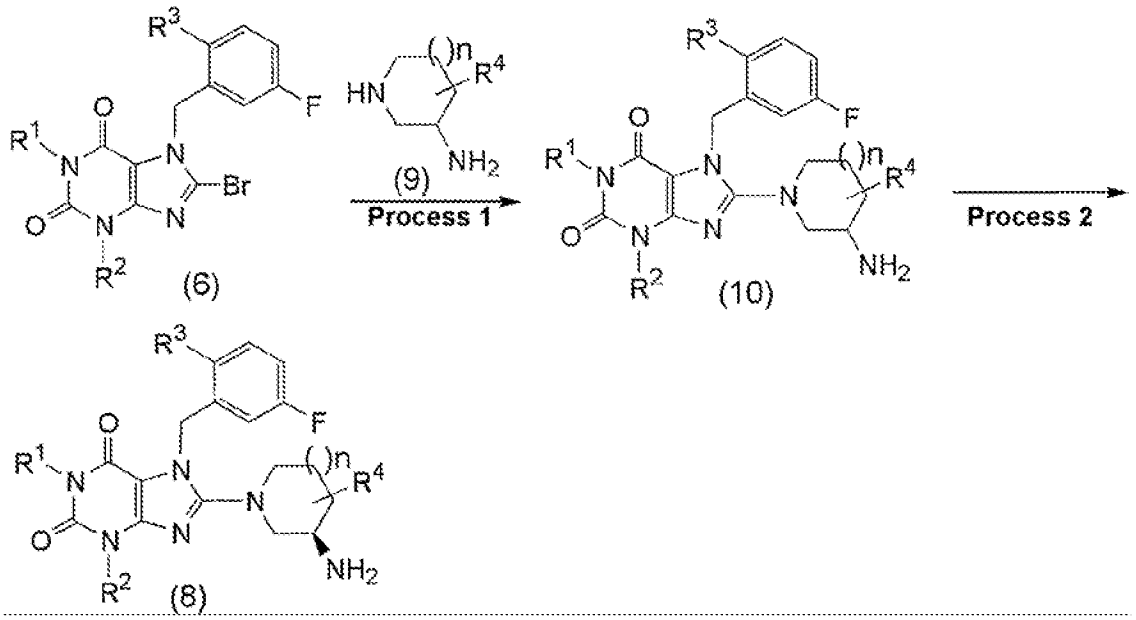
The compound (6) may be produced by allowing the compound (4) to react with the compound (5) in an inactive solvent in the presence of a base. The amount of the compound (5) used may be selected in the range of 1 to 3 weight equivalents to compound (4). Examples of the base include alkali carbonate (potassium carbonate, sodium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, and the like), alkali hydroxide (potassium hydroxide, sodium hydroxide, and the like), alkali hydride (sodium hydride, potassium hydride, and the like), alkoxy alkali (tert-butoxy potassium, and the like), etc.; and potassium carbonate, sodium hydride, and the like are preferable. The amount of the base used may be selected in the range of 1 to 5 weight equivalents to compound (4). Inactive solvents include non-protic solvents (dimethylformamide, dimethylsulfoxide, and the like) ether (diethylether, tetrahydrofuran, 1,4-dioxane, and the like), ketone (acetone, and the like), and mixtures of these, etc.; and dimethylformamide, and the like is preferable. The reaction temperature may be selected in the range of approximately 10°C to approximately 100°C.

4) Process 4

The compound (8) may be produced by allowing the compound (6) to react with the compound (7) in an inactive solvent with or without the presence of a base. Examples of the base include diisopropylethylamine, triethylamine, pyridine, 4-(dimethylamino)pyridine, N-methylmorpholine, and the like; and diisopropylethylamine, triethylamine, and the like are preferable. The amount of the base used may be selected in the range of 1 to 5 weight equivalents to compound (6). Inactive solvents include alcohol (ethanol, methanol, isopropanol, and the like), ether (1,4-dioxane, and the like), and mixtures of these, etc. The reaction temperature may be selected in the range of approximately 50°C to approximately 150°C. Moreover, the reaction may be conducted in a sealed reaction vessel such as an autoclave.

Production Method 2

Among the compounds represented by formula (I), the compound represented by formula (8) or a salt thereof can, for example, be produced by the method depicted below.




[In the formula, $R^1$, $R^2$, $R^3$, $R^4$, and n are the same as above.]

1) Process 1

Compound (10) may be produced from the compound (6) by the same method as that of Process 4 of Production Method 1.

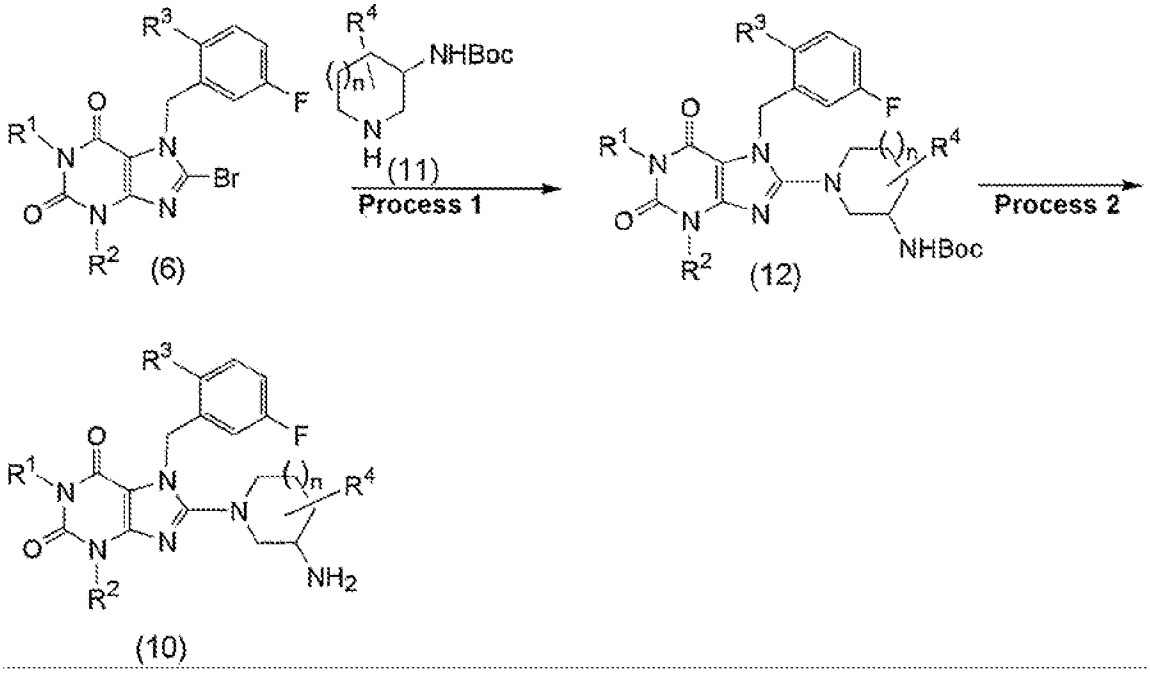
2) Process 2

Compound (8) may be produced by optical resolution of compound (10). Optical resolution can be conducted by dissolving compound (10) in an inactive solvent (for example, alcohol solvents such as methanol, ethanol, or 2-propanol; ether solvents such as diethylether; ester solvents such as ethyl acetate; hydrocarbon solvents such as toluene; or acetonitryl and the like, or mixtures of these), and by forming into optically active acids (for example, a monocarbonic acid such as mandelic acid, N-benzyloxyalanine, or lactic acid; a dicarbonic acid such as tartaric acid, o-diisopropylidene tartrate, or malic acid, or a sulfonic acid such as camphorsulfonic acid or bromocamphorsulfonic acid) and salts. The temperature at which the salt is formed is in the range from room temperature to the boiling point of the solvent. In order to improve the optical purity, it is desirable to raise the temperature close to the boiling point of the solvent. The yield may be improved by cooling as necessary prior to filtering out the precipitated salt. The suitable amount of optically active acid or amine used is in the range of approximately 0.5 to approximately 2.0 weight equivalents to the substrate, preferably, in the range of more or less 1 weight equivalent. Highly pure optically active salt can be obtained by re-crystallizing the crystals as necessary using an inactive solvent (for example, alcohol solvents such as

methanol, ethanol, or 2-propanol; ether solvents such as diethylether; ester solvents such as ethyl acetate; hydrocarbon solvents such as toluene; or acetonitryl and the like, or mixtures of these). Using common methods, the obtained salts may be treated with an acid or base as necessary to obtain free substance. Moreover, compound (8) may be produced by separating out compound (10) using a commercial chiral column.

Production Method 3

Among the compounds represented by formula (I), the compound represented by formula (10) or a salt thereof can, for example, be produced by the method depicted below.




[In the formula, $R^1$, $R^2$, $R^3$, $R^4$, and n are the same as above.]

1) Process 1

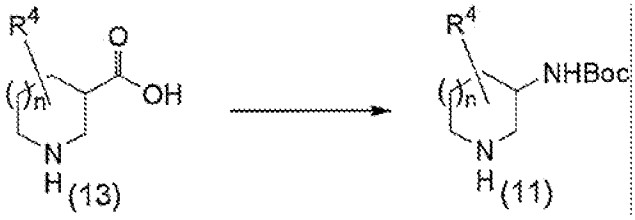
Compound (12) may be produced from the compound (6) by the same method as that of Process 4 of Production Method 1.

2) Process 2

The compound (10) may be produced by de-protecting the Boc group of the compound (12) in an inactive solvent in the presence of an acid. Examples of the acid include hydrochloric acid, sulfuric acid, or trifluoroacetic acid; and trifluoroacetic acid is preferable. The amount of the acid used may be selected in the range of 1 to 5 weight equivalents to compound (12). Inactive solvents include halogenated hydrocarbon solvents (dichloromethane, dichloroethane, chloroform, and the like), ether (1,4-dioxane, and the like), and mixtures of these, etc. The reaction temperature may be selected in the range of approximately -20°C to approximately 30°C.

Production Method 4

As indicated below, compound (11) may be produced from the compound (13) by following the method described, for example, in J. Org. Chem. 58, 879 (1993).




[In the formula, $R^4$ and n are the same as above.

Concrete examples of the synthesis of the compound (7) are indicated for compounds (7-1) to (7-9) below. Compounds (7-1) to (7-9) contain pharmaceutically permissible salts.

Table 13

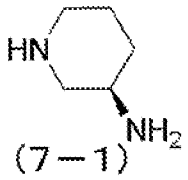
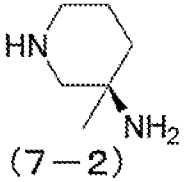
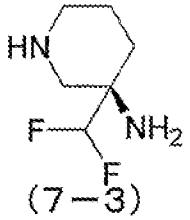
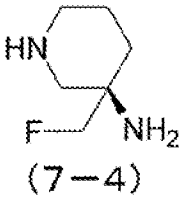
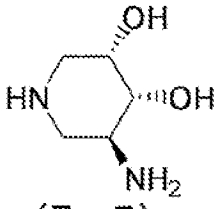
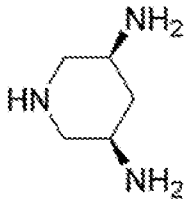
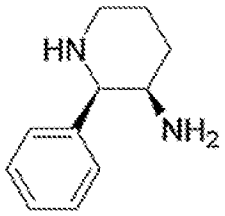
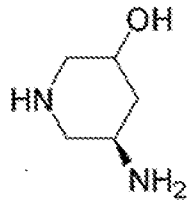
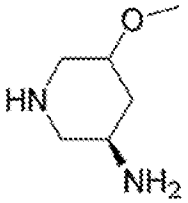
| Compound | Production Method |
|---|---|
|  (7－1) | WO 01/27082 |
|  (7－2) | Int. J. Peptide Protein Res. 40, 119 (1992)<br>WO 01/27082 |
|  (7－3) | US 4413141<br>WO 01/27082 |
|  (7－4) | Tetrahedron: Asymmetry 8, 327 (1997)<br>WO 01/27082 |
|  (7－5) | Tetrahedron: Asymmetry 11, 567 (2000) |

Table 14

| Compound | Production Method |
|---|---|
|  (7—6) | Chem. Eur. J. 6, 2830 (2000)<br>WO 00/26332 |
|  (7—7) | **Patent No. 2002-525325** |
|  (7—8) | Bull. Chem. Soc. Jpn. 53, 2605 (1980) |
|  (7—9) | **Using compound (7-8) as the starting material, follow the method described, for example, in the J. Am. Chem. Soc. 80, 2584 (1958), or J. Chem. Soc. PT1 499 (1972).** |

Concrete examples of the synthesis of the compound (7) are indicated for compounds (7-10) to (7-18) below. Compounds (7-10) to (7-18) contain pharmaceutically permissible salts.

Table 15

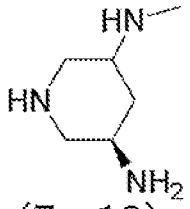
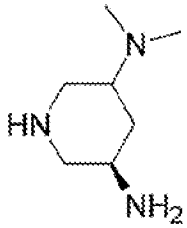
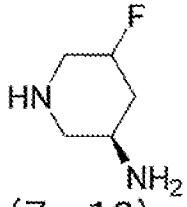
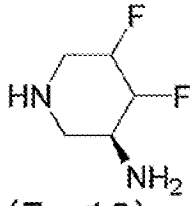
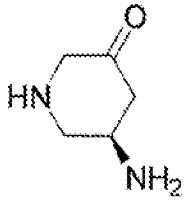
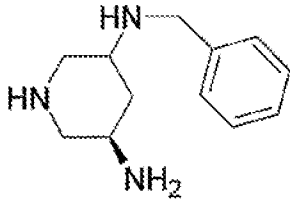
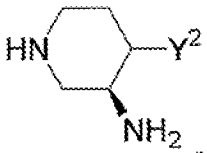
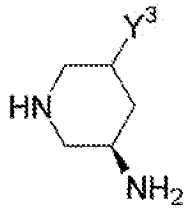
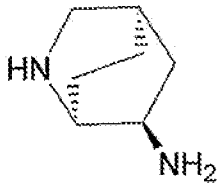
| Compound | Production Method |
|---|---|
|  (7－10) | Using compound (7-6) as the starting material, follow the method described, for example, in the J. Chem. Soc. Chem. Commun. 611 (1981). |
|  (7－11) | Using compound (7-6) as the starting material, follow the method described, for example, in the J. Chem. Soc. Chem. Commun. 611 (1981). |
|  (7－12) | Using compound (7-8) as the starting material, follow the method described, for example, in the J. Org. Chem. 44, 3872 (1979). |
|  (7－13) | Using compound (7-5) as the starting material, follow the method described, for example, in the J. Org. Chem. 44, 3872 (1979). |
|  (7－14) | Using compound (7-8) as the starting material, follow the method described, for example, in the Bull. Chem. Soc. Jpn. 64, 2857 (1991). |

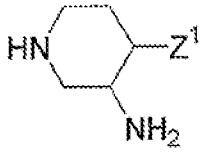
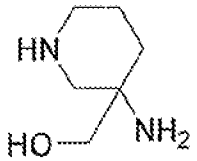
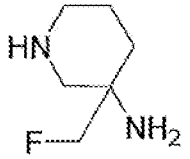
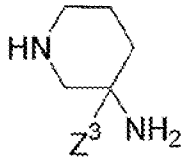
Table 16

| Compound | Production Method |
|---|---|
|  (7−15) | Using compound (7-6) as the starting material, follow the method described, for example, in Tetrahedron Lett. 40, 5609 (1999). |
|  (7−16A): $Y^2$ = (R)-$C_6H_5$ (7−16B): $Y^2$ = (S)-$C_6H_5$ | J. Med. Chem. 35, 833 (1992) and "Comprehensive Organic transformation", R.C. Larock, VCH publisher Inc., 1989. |
|  (7−17A): $Y^3$ = $NHS(O)_2CH_3$ (7−17B): $Y^3$ = $NHC(O)CH_3$ (7−17C): $Y^3$ = $NHC(O)C_6H_5$ (7−17D): $Y^3$ = $N(CH_3)C(O)CH_3$ | Using compound (7-6) as the starting material, follow the method described, for example, in "Comprehensive Organic transformation", R.C. Larock, VCH publisher Inc., 1989. |
|  (7−18) | WO 02/068420 |

Additionally, the compound (7) may be synthesized from substituted D-ornithine. A concrete example of the method is described in "Comprehensive Organic transformation", R.C. Larock, VCH publisher Inc., 1989.

Concrete examples of the synthesis of the compound (9) are indicated for compounds (9-1A) to (9-4C) below. Compounds (9-1A) to (9-4C) contain pharmaceutically permissible salts.

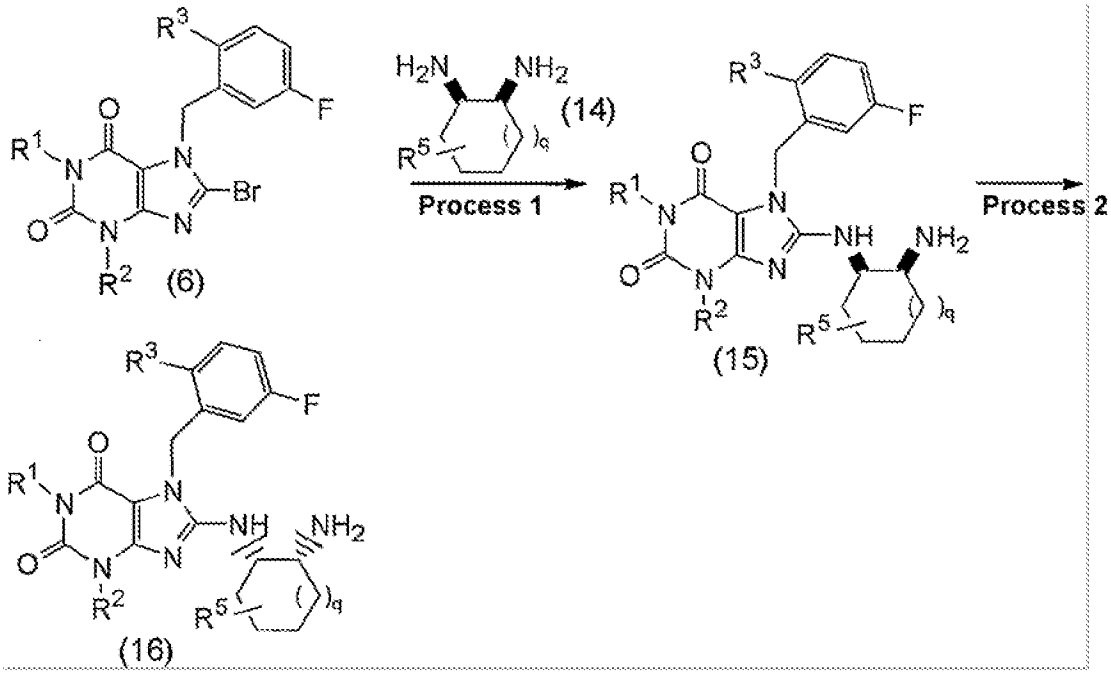
Table 17

| Compound | Production Method |
|---|---|
|  (9-1A): $Z^1 = CH_3$<br>(9-1B): $Z^1 = CH_2CH_3$<br>(9-1C): $Z^1 = CH_2CH_2OH$<br>(9-1D): $Z^1 = CH_2CH_2F$<br>(9-1E): $Z^1 = H$ | WO 02/48138 |
|  (9-2) | J. Org. Chem. 44, 2732 (1979) |
|  (9-3) | **Using compound (9-2) as the starting material, follow the method described, for example, in the J. Org. Chem. 44, 3872 (1979).** |
|  (9-4A): $Z^3 = CH_3$<br>(9-4B): $Z^3 = CH_2CH_3$<br>(9-4C): $Z^3 = CH_2CH_2CH_3$ | Arch. Pharm. 322, 499 (1989) |

A commercial product may used for the hydrochloride in the compound (9-1E). The compound (9) may be synthesized from substituted DL-ornithine using well-known methods. A concrete example of the method is described in "Comprehensive Organic transformation", R.C. Larock, VCH publisher Inc., 1989.

Production Method 5

Among the compounds represented by formula (I), the compound represented by formula (16) or a salt thereof can, for example, be produced by the method depicted below.




[In the formula, $R^1$, $R^2$, $R^3$, $R^5$, and q are the same as above.]

1) Process 1

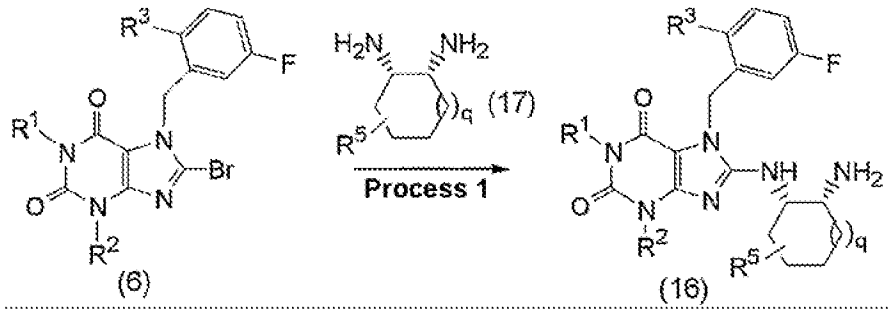
The compound (15) may be produced by allowing the compound (6) to react with the compound (14) in an inactive solvent with or without the presence of a base. Examples of the base include diisopropylethylamine, triethylamine, pyridine, 4-(dimethylamino)pyridine, N-methylmorpholine, and the like; and diisopropylethylamine, and the like is preferable. The amount of the base used may be selected in the range of 1 to 10 weight equivalents to compound (6). Inactive solvents include N-methyl-2-piperidone, dimethylformamide, toluene, and mixtures of these, etc. Preferably, N-methyl-2- piperidone and the like is used. The reaction temperature may be selected in the range of approximately 50°C to approximately 200°C. In addition, the reaction may be conducted in a sealed reaction vessel such as an autoclave.

2) Process 2

Compound (16) may be produced by optical resolution of compound (15). Optical resolution can be conducted by dissolving compound (15) in an inactive solvent (for example, alcohol solvents such as methanol, ethanol, or 2-propanol; ether solvents such as diethylether; ester solvents such as ethyl acetate; hydrocarbon solvents such as toluene; or acetonitryl and the like, or mixtures of these), and by forming into optically active acids (for example, a monocarbonic acid such as mandelic acid, N-benzyloxyalanine, or lactic acid; a dicarbonic acid such as tartaric acid, o-diisopropylidene tartrate, or malic acid; or a sulfonic acid such as camphorsulfonic acid or bromocamphorsulfonic acid) and salts. The temperature at which the salt is formed is in the range from room temperature to the boiling point of the solvent. In order to improve the optical purity, it is desirable to raise the temperature close to the boiling point of the solvent. The yield may be improved by cooling as necessary prior to filtering out the precipitated salt. The amount of optically active acid or amine used is suitable in the range of approximately 0.5 to approximately 2.0 weight equivalents to the substrate, preferably, in the range of more or less 1 weight equivalent. Highly pure optically active salt can be obtained by re-crystallizing the crystals as necessary using an inactive solvent (for example, alcohol solvents such as methanol, ethanol, or 2-propanol; ether solvents such as diethylether; ester solvents such as ethyl acetate, hydrocarbon solvents such as toluene; or acetonitryl and the like, or mixtures of these). Using common methods, the obtained salts may be treated with an acid or base as necessary to obtain free substance. Moreover, compound (16) may be produced by separating out compound (15) using a commercial chiral column.

Production Method 6

Among the compounds represented by formula (I), the compound represented by formula (16) or a salt thereof can, for example, be produced by the method depicted below.



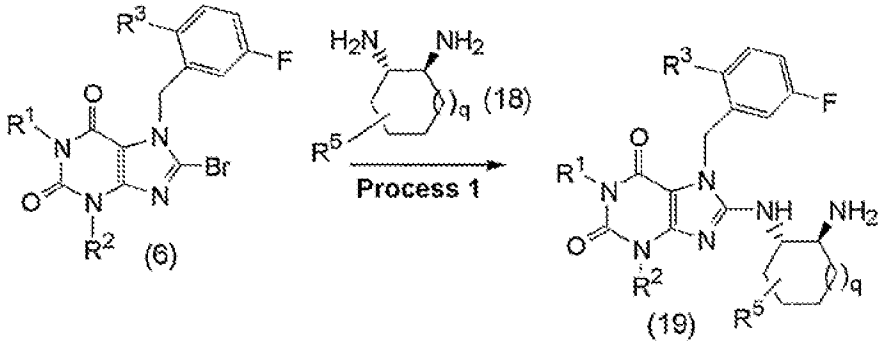

[In the formula, $R^1$, $R^2$, $R^3$, $R^5$, and q are the same as above.]

1) Process 1

Compound (16) may be produced from the compound (6) using the same method as that in Process 1 of Production Method 5. If necessary, the compound (16) may be separated as optically active substance by the same method as that in Process 2 of Production Method 5.

Production Method 7

Among the compounds represented by formula (I), the compound represented by formula (19) or a salt thereof can, for example, be produced by the method depicted below.



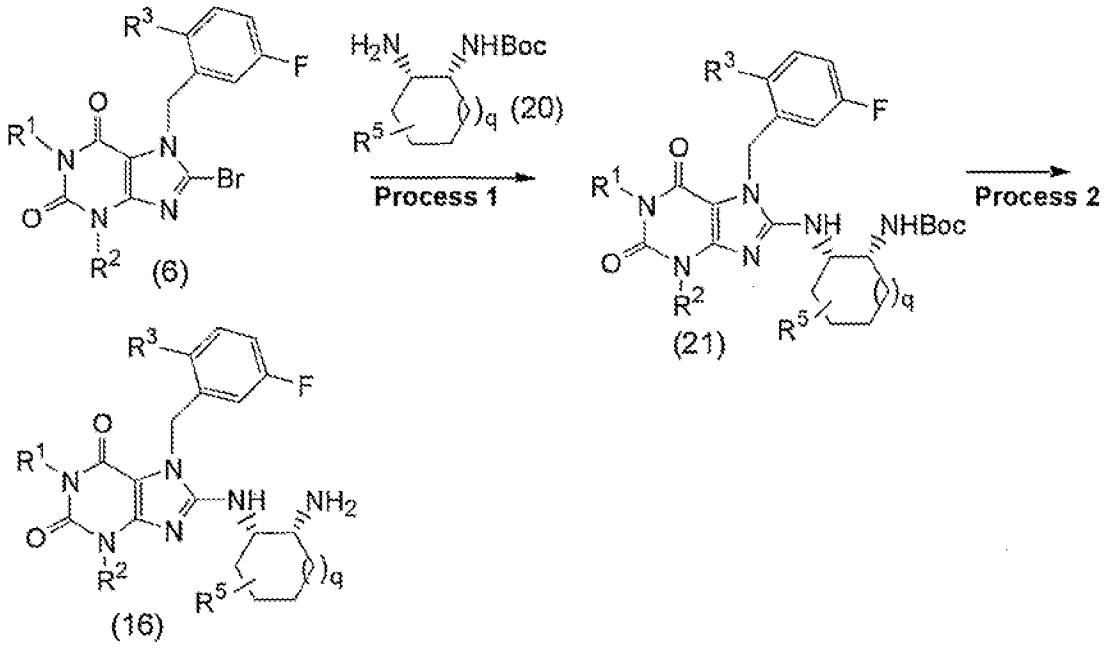

[In the formula, $R^1$, $R^2$, $R^3$, $R^5$, and q are the same as above.]

1) Process 1

Compound (19) may be produced from the compound (6) using the same method as that in Process 1 of Production Method 5.

Production Method 8

Among the compounds represented by formula (I), the compound represented by formula (16) or a salt thereof can, for example, be produced by the method depicted below.




[In the formula, $R^1$, $R^2$, $R^3$, $R^5$, and q are the same as above.]

1) Process 1

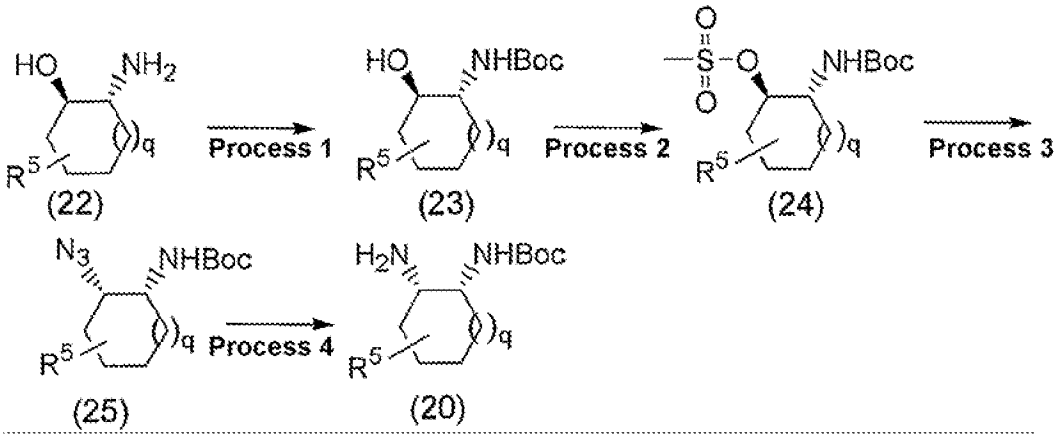
Compound (21) may be produced from the compound (6) using the same method as that in Process 1 of Production Method 5.

2) Process 2

The compound (16) may be produced by de-protecting the Boc group of the compound (21) in an inactive solvent in the presence of an acid. Examples of the acid include hydrochloric acid, sulfuric acid, or trifluoroacetic acid; and trifluoroacetic acid is preferable. The amount of the acid used may be selected in the range of 1 to 5 weight equivalents to compound (21). Examples of inactive solvents include halogenated hydrocarbon solvents (dichloromethane, dichloroethane, chloroform, and the like), ether (1,4-dioxane, and the like), and mixtures of these, etc. The reaction temperature may be selected in the range of approximately -20°C to approximately 30°C.

Production Method 9

As indicated below, compound (20) may be produced from the compound (22) by following the method described, for example, in J. Org. Chem. 50, 4154 (1985).

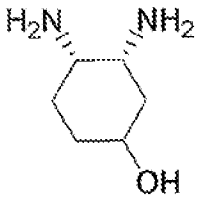



[In the formula, $R^5$ and q are the same as above.]

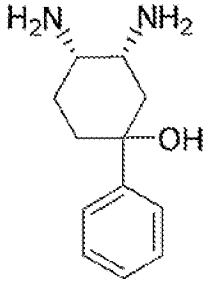
All the processes from processes 1 to 4 can be conducted by referring to the method described in "Comprehensive Organic transformation", R.C. Larock, VCH publisher Inc., 1989.

Production Method 10

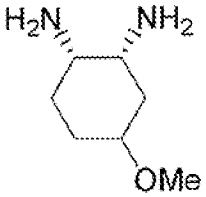
Concrete examples of the compound (17) include the following compounds (17-1) to (17-46). These compounds may be produced, for example, by following the methods described in WO 01/74774 and "Comprehensive Organic transformation", R.C. Larock, VCH publisher Inc., 1989.



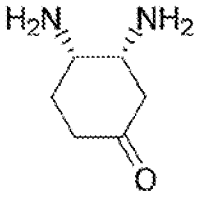

(17−1)



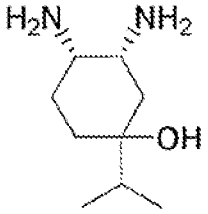

(17−6)



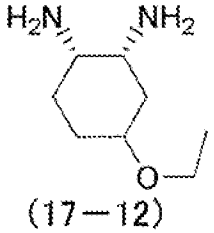

(17−11)




(17−2)




(17−7)

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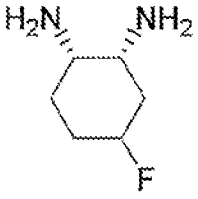
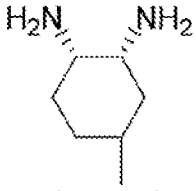
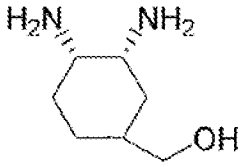


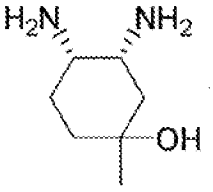

(17−3)



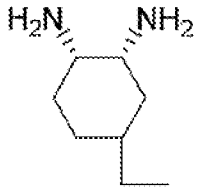

(17−8)



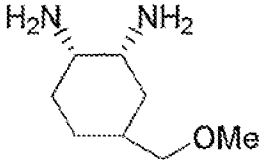

(17−13)




(17−4)




(17−9)

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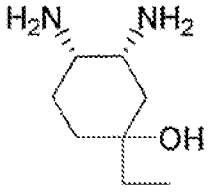
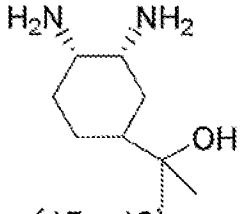
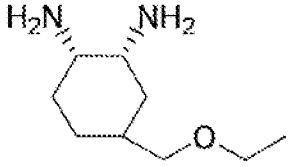


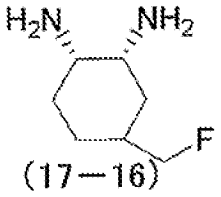

(17−5)




(17−10)




(17−15)



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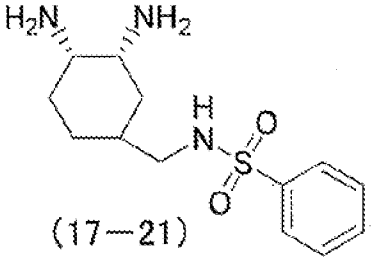
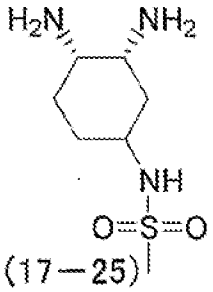
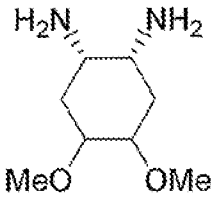


(17－21)



(17－25)



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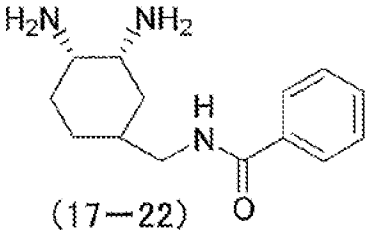

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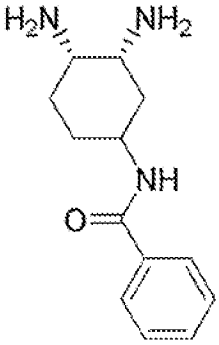
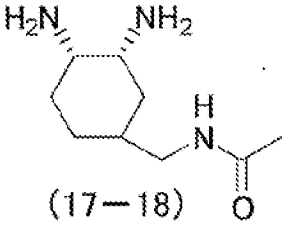


(17－26)



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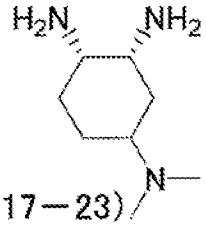

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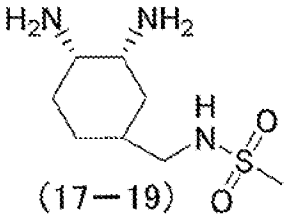

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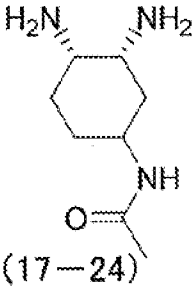
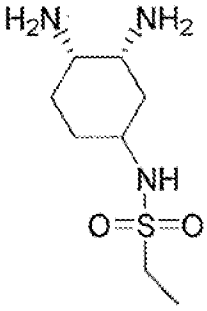
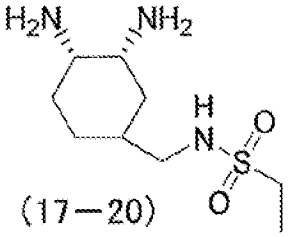


(17－24)



(17－27)



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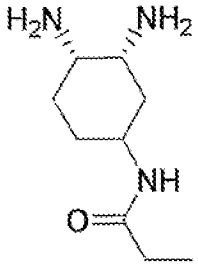

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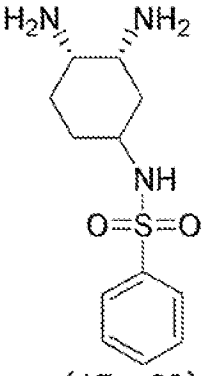

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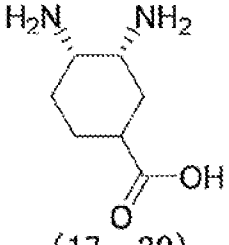

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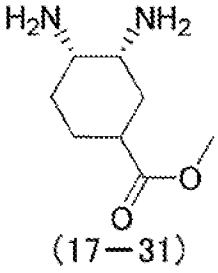
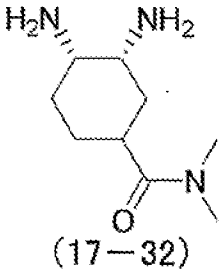
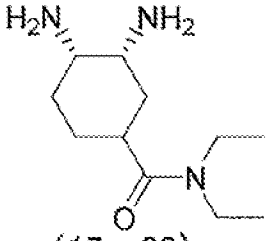


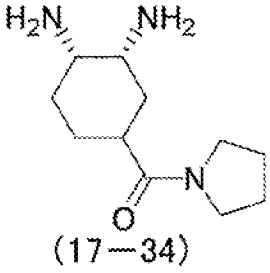
(17－31)



(17－32)



(17－33)



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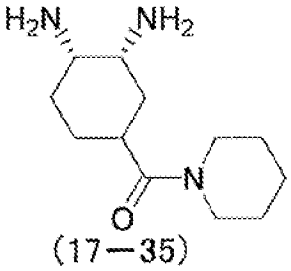

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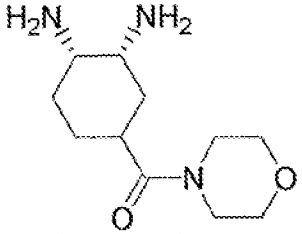
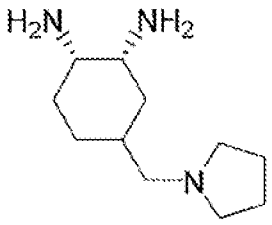
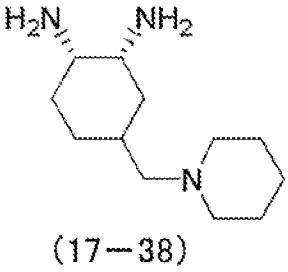


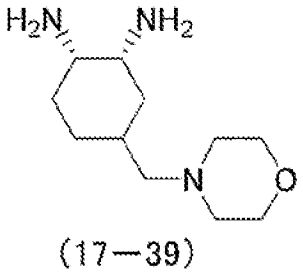
(17－36)



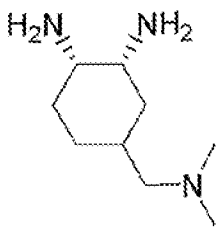
(17－37)



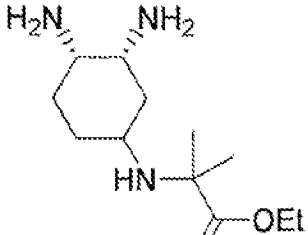
(17－38)



(17－39)




(17—40)

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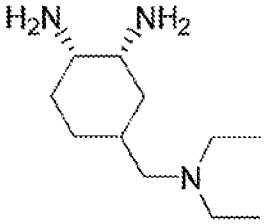


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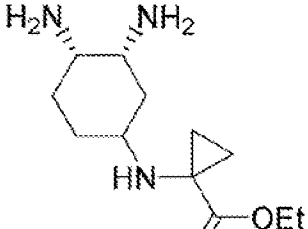
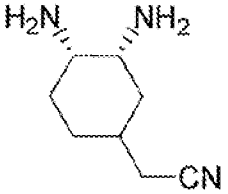
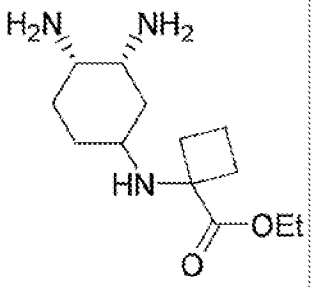


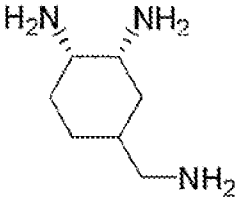

(17—45)




(17—42)




(17—46)




(17—43)

Commercial products may be used for the compounds (14) and (18).

If the compounds or intermediates of the present invention comprise a functional group such as an amino group, carboxy group, hydroxyl group, amidino group, guanidino group, or oxo group, a process to introduce a protective group or a process to remove protection may be included as necessary in the production method of the compounds of the present invention. The methods described in "Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc., 1991)" may be used for suitable protective groups, and for methods to protect and de-protect.

Examples of protective groups for hydroxyl groups include tert-butyldimethylsiryl

group, methoxymethyl group, and tetrahydropyranyl group; and examples of protective groups for amino groups include tert-butyloxycarbonyl group and benzyloxycarbonyl group. This kind of protective group for hydroxyl groups can be removed by reacting in a solvent such as aqueous methanol, aqueous ethanol, or aqueous tetrahydrofuran in the presence of an acid such as hydrochloric acid, sulfuric acid, or acetic acid. In addition, if a tert-butyldimethylsiryl group is used, for example, removal can be conducted in a solvent such as tetrahydrofuran in the presence of tetrabutylammonium fluoride. To remove the protective group for an amino group when a tert-butyloxycarbonyl group is used, for example, a reaction is conducted in a solvent such as methylene chloride, chloroform, or aqueous methanol in the presence of an acid such as hydrochloric acid, or trifluoroacetic acid, and a benzyloxycarbonyl group is removed, for example, by reacting in a solvent such as acetic acid in the presence of an acid such as hydrobromic acid.

Forms of protection when protecting carboxyl groups include, for example, tert-butylester, orthoester, and acid amide. Tert-butylester protective group is removed by reacting in an aqueous solvent in the presence of hydrochloric acid; orthoester is removed by dissolving in a solvent such as aqueous methanol, aqueous tetrahydrofuran, or aqueous 1,2-dimethoxyethane, and then treating with an alkali such as sodium hydroxide; and acid amide is removed, for example, by reacting in a solvent such as water, aqueous methanol, or aqueous tetrahydrofuran in the presence of an acid such as sulfuric acid.

Prodrugs can be produced by following common methods.

The xanthine compounds represented by formula (I) include substances having an optically active core, consequently, these racemic substances may be obtained in optically active form if optically active starting materials are used. If necessary, the racemic substance obtained may be physically or chemically divided into optical enantiomers using well-known methods. Preferably, diastereomers are formed from the racemic substance based on a reaction using an optically active resolving agent. Division into diastereomers of different forms may be achieved by well-known methods such as, for example, fractional crystallization.

The xanthine compound and the prodrug thereof may, for example, be made into a salt by dissolving in a solvent such as water, methanol, ethanol, or acetone, and mixing with a pharmaceutically permissible acid. Examples of pharmaceutically permissible acids include inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and nitric acid, or organic acids such as acetic acid, propionic acid, oxalic acid, succinic acid, lactic acid, malic acid, tartaric acid, citric acid, maleic acid, fumaric acid, methanesulfonic acid, p-toluenesulfonic acid or ascorbic acid.

The pharmaceutical agent of the present invention may be applied to the treatment of a variety of diseases based on an action to inhibit DPP-IV. The compounds in the present Description are useful in the suppression of postprandial hyperglycemia in the pre-diabetic state, treatment of non-insulin-dependent diabetes, treatment of auto-immune diseases such as arthritis and rheumatoid arthritis, treatment of diseases of the gastrointestinal mucosa, promotion of growth, suppression of transplanted organ rejection reaction, treatment of obesity, treatment of eating disorders, treatment of HIV infection, suppression of tumor metastasis, treatment of prostatomegaly, treatment of dental periostitis, and the treatment of osteoporosis.

When used therapeutically, the xanthine compound of the present invention, prodrug thereof or pharmaceutically permissible salt of either may be administered orally or non-orally (for example, intravenously, hypodermically, by intramuscular injection, locally, transrectally, transcutaneously, or transnasally) as a pharmaceutical composition. Examples of orally administered compositions include tablets, capsules, pills, granules, powders, liquids and suspensions; and examples of non-orally administered compositions include aqueous agents for injection, oils, ointments, creams, lotions, aerosols, suppositories, and patches. These preparations may be prepared using conventional, well-known technologies, and may contain the non-toxic and inactive carriers and excipients commonly used in the field of medical preparations.

The dosage may very depending on the individual compound, and depending on the disease, age, weight, sex, and symptoms of the patient, and on the administration route, but normally for adults (weight 50kg), 0.1 to 1000 mg/day, preferably 1 to 300 mg/day, of the xanthine compound of the present invention, prodrug thereof or pharmaceutically permissible salt of either is administered once daily or divided into 2 to 3 doses. Moreover, administration can be divided into once every several days or several weeks.

Moreover, the xanthine compound of the present invention, prodrug thereof or pharmaceutically permissible salt of either may be concomitantly used with other agents to treat diabetes. Here, examples of other agents to treat diabetes includes insulin preparations, sulfonylurea drugs, sulfonamide drugs, insulin secretion promoters, biguanide drugs, α-glucosidase inhibitors, and drugs to alleviate insulin resistance.

Embodiments

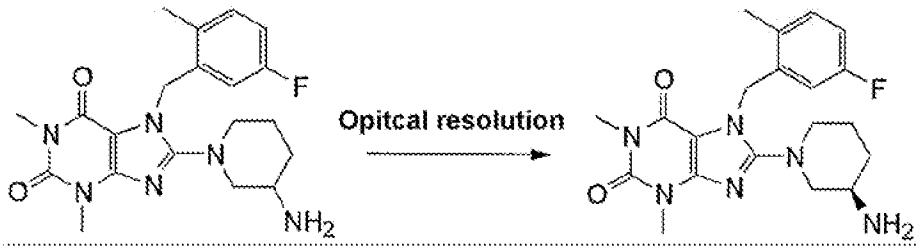
The present invention will be explained in detail below using reference examples and embodiments, but the present invention is not limited to these. Further, the following abbreviations may be used in order to simplify the present Description:

Boc: tert-butoxycarbonyl group

Cbz: Benzyloxycarbonyl group

Embodiment 1

1,3-dimethyl-7-(2-methyl-5-fluorobenzyl)-8-((R)-3-aminopiperidin-1-yl)xanthine




5.0 mg of the compound of Embodiment 1 was obtained by optically resolving the compound of Embodiment 6 using an optically active column under the following separation conditions.

Separation conditions:

| | |
|---|---|
| Column: | CHIRALPAK AD-H (DAICEL) (Φ2.0 cm x 25.0 cm) |
| Mobile phase: | 34% 2-propanol / 65.8% hexane / 0.2% diethylamine |
| Detection wavelength (UV): | 254 nm |
| Flow rate: | 5.0 ml/min |

Retention time: 36.98 min (CHIRALPAK AD-H: 34% 2-propanol / hexane / 0.2 vol %

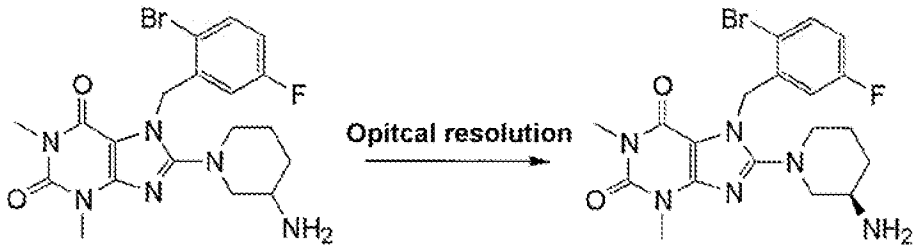
diethylamine)

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.16-7.12 (m, 1H), 6.89-6.84 (m, 1H), 6.45-6.41 (m, 1H), 5.32 (d, J = 16.8 Hz, 1H), 5.27 (d, J = 16.8 Hz, 1H), 3.58 (s, 3H), 3.40-3.35 (m, 1H), 3.34 (s, 3H), 3.26-3.23 (m, 1H), 2.93-2.88 (m, 2H), 2.74-2.68 (m, 1H), 2.33 (s, 3H), 1.95-1.88 (m, 1H), 1.75-1.68 (m, 1H), 1.60-1.56 (m, 1H), 1.26-1.22 (m, 1H).

MS (ESI+) 401 ($M^+$+1, 100%).

Embodiment 2

1,3-dimethyl-7-(2-bromo-5-fluorobenzyl)-8-((R)-3-aminopiperidin-1-yl)xanthine



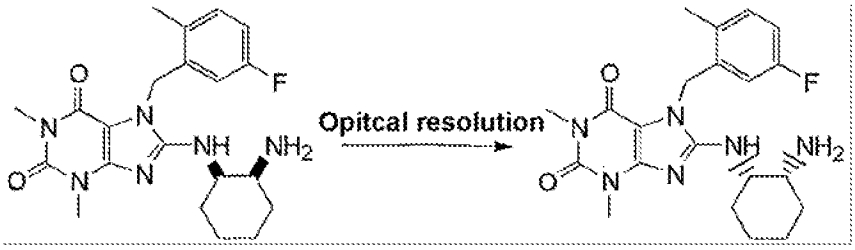

3.7 mg of the compound of Embodiment 2 was obtained from the compound of Embodiment 7 using the same method as that of Embodiment 1. Retention time: 38.16 min (CHIRALPAK AD-H: 34% 2-propanol / hexane / 0.2 vol% diethylamine)

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.58-7.54 (m, 1H), 6.93-6.87 (m, 1H), 6.59-6.55 (m, 1H), 5.38 (d, J = 17.7 Hz, 1H), 5.34 (d, J = 17.7 Hz, 1H), 3.58 (s, 3H), 3.39-3.38 (m, 1H), 3.36 (s, 3H), 3.26-3.22 (m, 1H), 2.94-2.90 (m, 2H), 2.71-2.66 (m, 1H), 1.97-1.89 (m, 1H), 1.78-1.70 (m, 1H), 1.61-1.57 (m, 1H), 1.26-1.23 (m, 1H).

MS (ESI+) 465 ($M^+$+1, 100%).

Embodiment 3

1,3-dimethyl-7-(2-methyl-5-fluorobenzyl)-8-{[ ((1S, 2R)-2-aminocyclohexyl)amino]xanthine




6 mg of the compound of Embodiment 3 was obtained by optically separating the compound of Embodiment 18 using an optically active column under the following separation conditions.

Separation conditions:

| | |
|---|---|
| Column: | CHIRALPAK AD-H (DAICEL) (Φ2.0 cm x 25.0 cm) |
| Mobile phase: | 34% 2-propanol / 65.8% hexane / 0.2% diethylamine |
| Detection wavelength (UV): | 254 nm |
| Flow rate: | 5.0 ml/min |

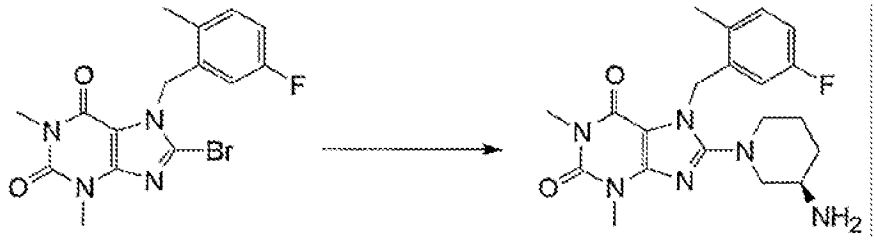
Retention time: 22.13 min (CHIRALPAK AD-H: 34% 2-propanol / hexane / 0.2 vol % diethylamine)

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.17-7.14 (m, 1H), 6.92-6.87 (m, 1H), 6.63-6.60 (m, 1H), 5.35 (s, 2H), 4.97 (d, J = 7.2 Hz, 1H), 3.84-3.78 (m, 1H), 3.55 (s, 3H), 3.37 (s, 3H), 2.99-2.96 (m, 1H), 2.33 (s, 3H), 1.70-1.66 (m, 1H), 1.59-1.56 (m, 1H), 1.40-1.25 (m, 6H).

MS (ESI+) 415 ($M^+$+1, 100%).

Embodiment 4

1,3-dimethyl-7-(2-methyl-5-fluorobenzyl)-8-((R)-3-aminoaminopiperidin-1-yl)xanthine



An ethanol solution (6 mL) of 1,3 dimethyl-7-(2-methyl-5-fluorobenzyl)-8-bromoxanthine (152 mg) and (R)-3-aminopiperidine (100 mg) was sealed in a tube,

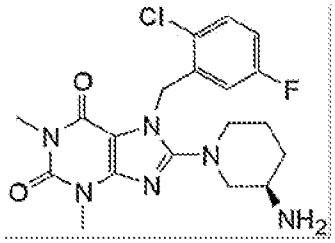
heated to 110°C and agitated for 20 hours. After cooling the reaction solution to 25°C, vacuum concentration was conducted, saturated sodium bicarbonate water was added to the residue and extraction was conducted 3 times with chloroform (30 mL). After the organic layer was dried with anhydrous sodium sulfate and filtered, vacuum concentration was conducted, the residue was refined using silica gel column chromatography (development solvent: chloroform / methanol = from 100/1 to 20/1), and compound of Embodiment 4 (124 mg) was obtained as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.16-7.12 (m, 1H), 6.89-6.84 (m, 1H), 6.45-6.41 (m, 1H), 5.32 (d, J = 16.8 Hz, 1H), 5.27 (d, J = 16.8 Hz, 1H), 3.58 (s, 3H), 3.40-3.35 (m, 1H), 3.34 (s, 3H), 3.26-3.23 (m, 1H), 2.93-2.88 (m, 2H), 2.74-2.68 (m, 1H), 2.33 (s, 3H), 1.95-1.88 (m, 1H), 1.75-1.68 (m, 1H), 1.60-1.56 (m, 1H), 1.26-1.22 (m, 1H).

MS (ESI+) 401 ($M^+$+1, 100%).

Embodiment 5

1,3-dimethyl-7-(2-chloro-5-fluorobenzyl)-8-((R)-3-aminopiperidin-1-yl)xanthine



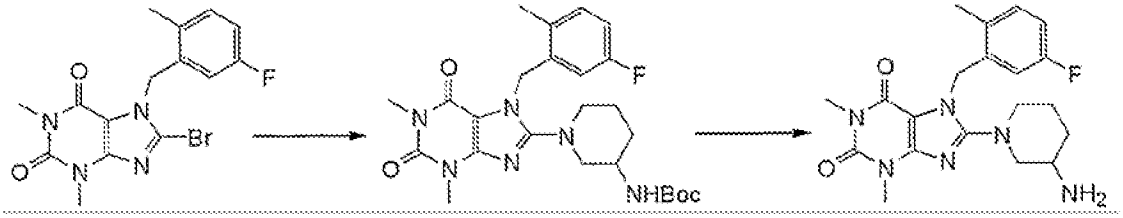

The compound of Embodiment 5 synthesized from the corresponding reference compound using the same method as that of Embodiment 4.

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.40-7.36 (m, 1H), 6.98-6.93 (m, 1H), 6.61-6.58 (m, 1H), 5.38 (d, J = 17.6 Hz, 1H), 5.33 (d, J = 17.6 Hz, 1H), 3.58 (s, 3H), 3.40-3.38 (m, 1H), 3.35 (s, 3H), 3.25-3.22 (m, 1H), 2.94-2.91 (m, 2H), 2.73-2.68 (m, 1H), 1.93-1.90 (m, 1H), 1.73-1.72 (m, 1H), 1.61-1.57 (m, 1H), 1.27-1.24 (m, 1H).

MS (ESI+) 421 ($M^+$+1, 100%).

Embodiment 6

1,3-dimethyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)xanthine




An ethanol solution (6 mL) of 1,3 dimethyl-7-(2-methyl-5-fluorobenzyl)-8-bromoxanthine (191 mg) and 3-[(tert-butoxycarbonyl)amino]piperidine (200 mg) was sealed in a tube, heated to 100° C and agitated for 30 hours. After cooling the reaction solution to 25°C, vacuum concentration was conducted. The residue was refined using silica gel column chromatography (development solvent: chloroform / methanol = from 200/1 to 75/1), and the product was obtained. Next, 4N hydrochloric acid/dioxane solution (20 mL) was added to the xanthine solution of the present product (4 mL), and this was agitated for 3 hours at 25°C. Vacuum concentration was conducted on the reaction solution, saturated sodium bicarbonate water (100mL) was added to the residue, and extraction was conducted 3 times using chloroform (30 mL). After the organic layer was dried with anhydrous sodium sulfate and filtered, vacuum concentration was conducted, and the compound of Embodiment 6 (204 mg) was obtained as a white solid.

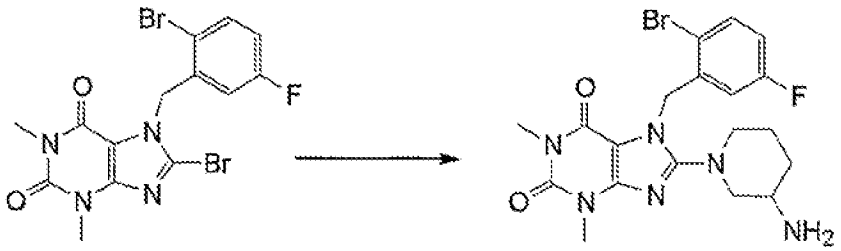
$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.16-7.13 (m, 1H), 6.89-6.84 (m, 1H), 6.44-6.41 (m, 1H), 5.32 (d, J = 16.7 Hz, 1H), 5.26 (d, J = 16.7 Hz, 1H), 3.58 (s, 3H), 3.40-3.36 (m, 1H), 3.34 (s, 3H), 3.26-3.22 (m, 1H), 2.95-2.88 (m, 2H), 2.75-2.69 (m, 1H), 2.33 (s, 3H), 1.95-1.88 (m, 1H), 1.71-1.69 (m, 1H), 1.62-1.58 (m, 1H), 1.26-1.21 (m, 1H).

MS (ESI+) 401 ($M^+$+1, 100%).

The compounds of Embodiments 7 to 10 were synthesized from the various corresponding reference compounds using the same method as that in Embodiment 6.

Embodiment 7

1,3-dimethyl-7-(2-bromo-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)xanthine

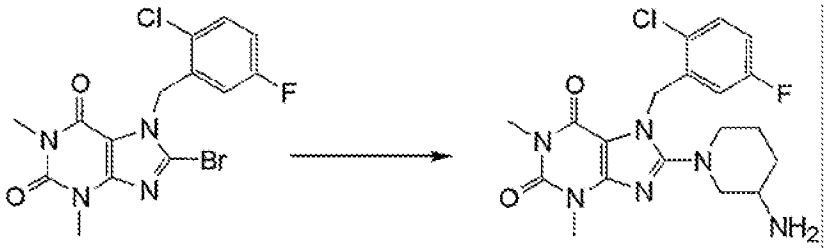


$^1$H NMR (400 MHz, $CDCl_3$) δ 7.58-7.54 (m, 1H), 6.93-6.88 (m, 1H), 6.59-6.56 (m, 1H), 5.38 (d, J = 17.0 Hz, 1H), 5.34 (d, J = 17.0 Hz, 1H), 3.58 (s, 3H), 3.40-3.38 (m, 1H), 3.36 (s, 3H), 3.26-3.22 (m, 1H), 2.93-2.88 (m, 2H), 2.71-2.66 (m, 1H), 1.93-1.89 (m, 1H), 1.75-1.71 (m, 1H), 1.61-1.57 (m, 1H), 1.29-1.20 (m, 1H).

MS (ESI+) 465 ($M^+$+1, 96%).

Embodiment 8

1,3-dimethyl-7-(2-chloro-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)xanthine

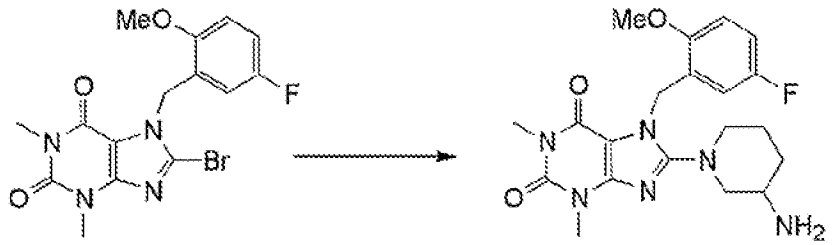


$^1$H NMR (400 MHz, $CDCl_3$) δ 7.39-7.36 (m, 1H), 6.98-6.93 (m, 1H), 6.61-6.58 (m, 1H), 5.38 (d, J = 17.6 Hz, 1H), 5.33 (d, J = 17.6 Hz, 1H), 3.58 (s, 3H), 3.40-3.38 (m, 1H), 3.36 (s, 3H), 3.25-3.22 (m, 1H), 2.95-2.88 (m, 2H), 2.72-2.67 (m, 1H), 1.93-1.90 (m, 1H), 1.73-1.70 (m, 1H), 1.61-1.57 (m, 1H), 1.25-1.23 (m, 1H).

MS (ESI+) 421 ($M^+$+1, 100%).

Embodiment 9

1,3-dimethyl-7-(2-methoxy-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)xanthine

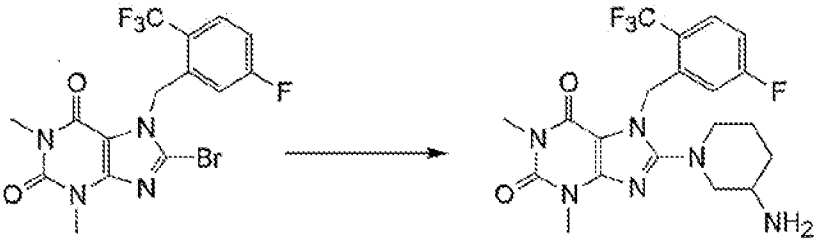


$^1$H NMR (400 MHz, $CDCl_3$) δ 6.95-6.90 (m, 1H), 6.83-6.81 (m, 1H), 6.53-6.49 (m, 1H), 5.36 (d, J = 17.2 Hz, 1H) , 5.31 (d, J = 17.2 Hz, 1H), 3.86 (s, 3 H), 3.57 (s, 3H), 3.42-3.37 (m, 1H), 3.35 (s, 3H), 3.29-3.24 (m, 1H), 2.92 -2.87 (m, 2H), 2.73-2.67 (m, 1H), 1.94-1.88 (m, 1H), 1.75-1.68 (m, 1H), 1. 60-1.56 (m, 1H), 1.26-1.20 (m, 1H).

MS (ESI+) 417 ($M^+$+1, 100%).

Embodiment 10

1,3-dimethyl-7-(2-trifluoromethyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)xanthine



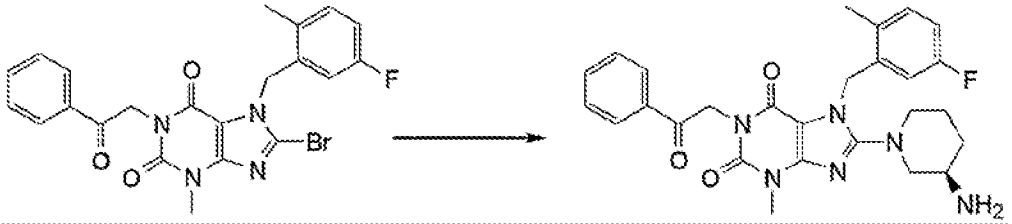
$^1$H NMR (400 MHz, $CDCl_3$) δ 7.74-7.71 (m, 1H), 7.09-7.05 (m, 1H), 6.66 (d, J = 9.0 Hz, 1H), 5.54 (s, 2H), 3.59 (s, 3H), 3.41-3.36 (m, 1H), 3.35 (s, 3H ), 3.23-3.19 (m, 1H), 2.91-2.84 (m, 2H), 2.70-2.65 (m, 1H), 1.93-1.89 (m, 1H), 1.69-1.67 (m, 1H), 1.58-1.54 (m, 1H), 1.25-1.21 (m, 1H).

MS (ESI+) 455 ($M^+$+1, 100%).

Embodiment 11

1-(2-oxo-2-phenylethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-((R)-3-aminopiperidin-

1-yl)xanthine



An ethanol solution (6 mL) of 1-(2-oxo-2-phenylethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-bromoxanthine (242 mg) and (R)-tert-3-butylpepiridin-3-yl carbamate (200 mg) was sealed in a tube, heated to 110°C and agitated for 30 hours. After cooling the reaction solution to 25°C, vacuum concentration was conducted. The residue was refined using silica gel column chromatography (development solvent: chloroform / methanol = from 200/1 to 75/1), and the product (350 mg) was obtained. Next, 4N hydrochloric acid/dioxane solution (20 mL) was added to the xanthine solution of the present product (5 mL), and this was agitated for 3 hours at 25°C. Vacuum concentration was conducted on the reaction solution, saturated sodium bicarbonate water (100 mL) was added to the residue, and extraction was conducted twice using chloroform (50 mL). After the organic layer was dried with anhydrous sodium sulfate and filtered, vacuum concentration was conducted, and the compound of Embodiment 11 (237 mg) was obtained as a white solid.

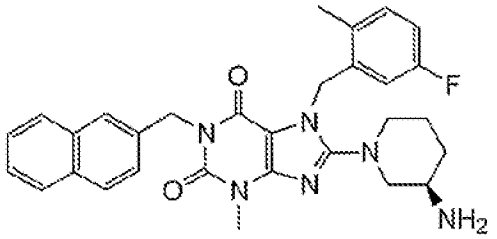
$^1$H NMR (400 MHz, $CDCl_3$) δ 8.00-7.97 (m, 2H), 7.59-7.56 (m, 1H), 7.50-7.44 (m, 2H), 7.13 (dd, J = 5.6, 8.3 Hz, 1H), 6.88-6.84 (m, 1H), 6.51 (dd, J = 2.5, 9.7 Hz, 1H), 5.40 (s, 2H), 5.30 (d, J = 16.8 Hz, 1H), 5.25 (d, J = 16.8 Hz, 1H), 3.60 (s, 3H), 3.45-3.38 (m, 1H), 3.30-3.23 (m, 1H), 2.95-2.91 (m, 2H), 2.76-2.71 (m, 1H), 2.30 (s, 3H), 1.97-1.90 (m, 1H), 1.76-1.70 (m, 1H), 1.65-1.60 (m, 1H), 1.30-1.22 (m, 1H).

MS (ESI+) 505 ($M^+$+1, 100%).

The compounds of Embodiments 12 to 14 were synthesized from the various corresponding reference compounds using the same method as that in Embodiment 11.

Embodiment 12

1-(2-napthylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-((R)-3-aminopiperidin-1-yl)xanthine

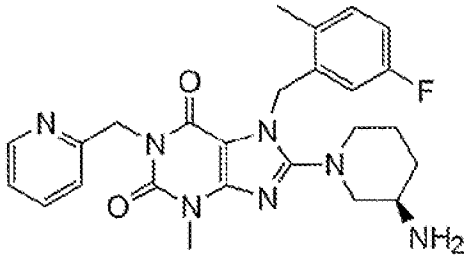


$^1$H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.79-7.73 (m, 3H), 7.55 (dd, J = 1.7, 8.4 Hz, 1H), 7.43-7.40 (m, 2H), 7.14-7.12 (m, 1H), 6.90-6.87 (m, 1H), 6.50 (dd, J = 2.6, 9.8 Hz, 1H), 5.36-5.26 (m, 4H), 3.56 (s, 3H), 3.39-3.35 (m, 1H), 3.25-3.22 (m, 1H), 2.92-2.86 (m, 2H), 2.73-2.68 (m, 1H), 2.32 (s, 3H), 1.94-1.88 (m, 1H), 1.75-1.68 (m, 1H), 1.62-1.55 (m, 1H), 1.25-1.19 (m, 1H).

MS (ESI+) 527 ($M^+$+1, 100%).

Embodiment 13

1-(pyridin-2-yl methyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-((R)-3-aminopiperidin-1-yl)xanthine

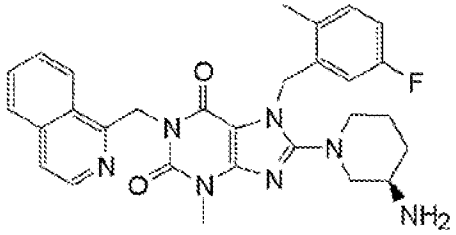


$^1$H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 4.2 Hz, 1H), 7.60-7.56 (m, 1H), 7.17 (d, J = 7.8 Hz, 1H), 7.14-7.09 (m, 2H), 6.88-6.84 (m, 1H), 6.48 (dd, J = 2.5, 9.8 Hz, 1H), 5.36-5.26 (m, 4H), 3.58 (s, 3H), 3.41-3.38 (m, 1H), 3.26-3.23 (m, 1H), 2.95-2.90 (m, 2H), 2.78-2.72 (m, 1H), 2.30 (s, 3H), 1.72-1.69 (m, 1H), 1.65-1.57 (m, 2H), 1.29-1.25 (m, 1H).

Embodiment 14

1-(isoquinolin-1-yl methyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-((R)-3-

aminopiperidin-1-yl)xanthine

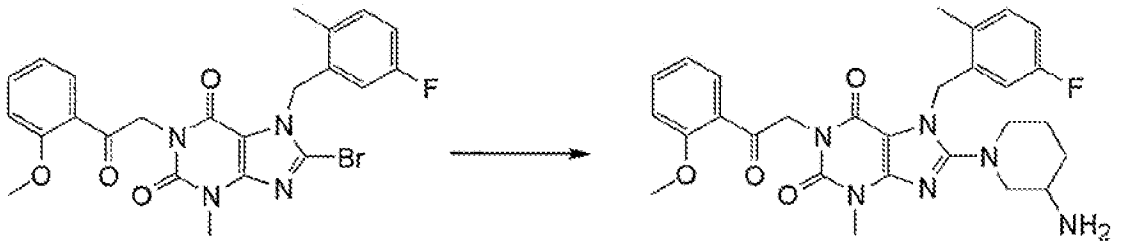


$^1$H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 5.8 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.65-7.58 (m, 2H), 7.48 (d, J = 5.7 Hz, 1H), 7.10-7.07 (m, 1H), 6.86-6.83 (m, 1H), 6.54 (dd, J = 2.5, 9.8 Hz, 1H), 5.82 (s, 2H), 5.33 (d, J = 17.1 Hz, 1H), 5.28 (d, J = 17.1 Hz, 1H), 3.62 (s, 3H), 3.42-3.38 (m, 1H), 3.28-3.23 (m, 1H), 2.94-2.90 (m, 2H), 2.76-2.71 (m, 1H), 2.28 (s, 3H), 1.94-1.90 (m, 1H), 1.75-1.70 (m, 1H), 1.61-1.55 (m, 1H), 1.26-1.23 (m, 1H).

MS (ESI+) 528 ($M^+$+1, 100%).

Embodiment 15

1-[2-oxo-2-(2-methoxyphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)xanthine



An ethanol solution (10 mL) of 1-[2-oxo-2-(2-methoxyphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-bromoxanthine (258 mg) and 3-aminopepiridine dihydrochloride (346 mg) was sealed in a tube, heated to 110°C and agitated for 8 hours. After cooling the reaction solution to 25°C, vacuum concentration was conducted. The residue was dissolved in chloroform (100 mL), and was rinsed with 1N hydrochloric acid (100 mL) and then in saturated sodium bicarbonate water (100 mL). The organic layer was dried with anhydrous sodium sulfate and filtered, vacuum concentration was conducted, and the compound of Embodiment 15 (186 mg) was obtained as a pale yellow

solid.

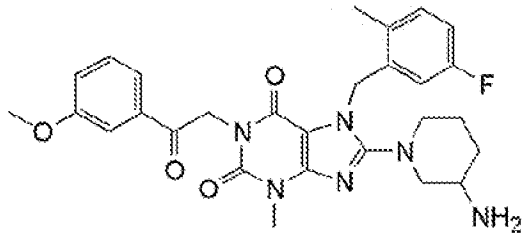
$^1$H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, J = 1.8, 7.8 Hz, 1H), 7.50-7.46 (m, 1H), 7.12 (dd, J = 5.7, 8.2 Hz, 1H), 7.01-6.96 (m, 2H), 6.86-6.83 (m, 1H), 6.50 (dd, J = 2.6, 9.7 Hz, 1H), 5.34 (s, 2H), 5.31-5.23 (m, 2H), 3.93 (s, 3H), 3.59 (s, 3H), 3.41-3.37 (m, 1H), 3.27-3.23 (m, 1H), 2.93-2.88 (m, 2H), 2.75-2.69 (m, 1H), 2.30 (s, 3H), 1.96-1.88 (m, 1H), 1.75-1.68 (m, 1H), 1.61-1.59 (m, 1H), 1.26-1.23 (m, 1H).

MS (ESI+) 535 ($M^+$+1, 100%).

The compounds of Embodiments 16 and 17 were synthesized from the various corresponding reference compounds using the same method as that in Embodiment 15.

Embodiment 16

1-[2-oxo-2-(3-methoxyphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-aminopiperidin-1-yl)xanthine



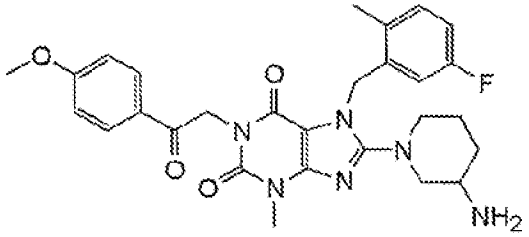

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.59-7.57 (m, 1H), 7.50-7.49 (m, 1H), 7.39-7.35 (m, 1H), 7.14-7.11 (m, 2H), 6.87-6.84 (m, 1H), 6.52-6.49 (m, 1H), 5.38 (s, 2H), 5.30 (d, J = 16.8 Hz, 1H), 5.25 (d, J = 16.8 Hz, 1H), 3.83 (s, 3H), 3.59 (s, 3H), 3.42-3.39 (m, 1H), 3.30-3.25 (m, 1H), 2.95-2.91 (m, 2H), 2.76-2.70 (m, 1H), 2.30 (s, 3H), 1.96-1.90 (m, 1H), 1.75-1.70 (m, 1H), 1.62-1.60 (m, 1H), 1.27-1.24 (m, 1H).

MS (ESI+) 535 ($M^+$+1, 100%).

Embodiment 17

1-[2-oxo-2-(4-methoxyphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-(3-

aminopiperidin-1-yl)xanthine

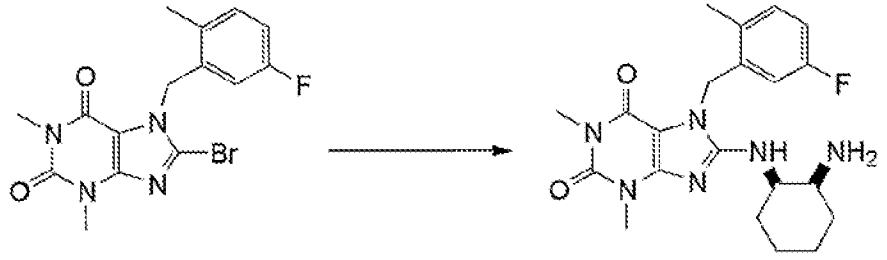


$^1$H NMR (400 MHz, $CDCl_3$) δ 7.98-7.95 (m, 2H), 7.12 (dd, J = 5.7, 8.3 Hz, 1H), 6.95-7.91 (m, 2H), 6.88-6.84 (m, 1H), 6.50 (dd, J = 2.6, 9.7 Hz, 1H), 5.36 (s, 2H), 5.30 (d, J = 16.7 Hz, 1H), 5.25 (d, J = 16.7 Hz, 1H), 3.87 (s, 3H), 3.59 (s, 3H), 3.42-3.38 (m, 1H), 3.29-3.23 (m, 1H), 2.96-2.89 (m, 2H), 2.75-2.70 (m, 1H), 2.29 (s, 3H), 1.95-1.88 (m, 1H), 1.75-1.69 (m, 1H), 1.64-1.61 (m, 1H), 1.27-1.24 (m, 1H).

MS (ESI+) 535 ($M^+$+1, 100%).

Embodiment 18

1,3-dimethyl-7-(2-methyl-5-fluorobenzyl)-8-[(cis-2-aminocyclohexyl)amino]xanthine



An N-methylpyrrolidinone solution (1.5 mL) of 1,3-dimethyl-7-(2-methyl-5-fluorobenzyl)-8-bromoxanthine (191 mg) and 1,2-cyclohexanediamine (171 mg) was sealed in a tube, heated to 160°C and agitated for 10 hours. After cooling the reaction solution to 25°C, vacuum concentration was conducted, 5% potassium carbonate water was added to the residue, and extraction was conducted 3 times using chloroform (30 mL). The organic layer was dried with anhydrous magnesium sulfate and filtered, and then vacuum concentration was conducted. This was refined by adding toluene (1.0 mL) and re-crystallizing, yielding the compound of Embodiment 18 (182 mg) as a white solid.

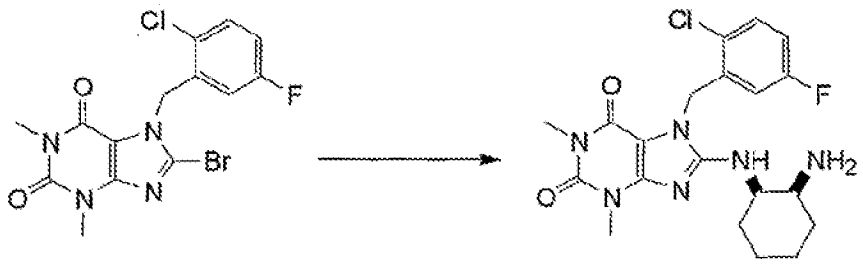
$^1$H NMR (400 MHz, $CDCl_3$) δ 7.17-7.13 (m, 1H), 6.91-6.86 (m, 1H), 6.63-6.60 (m, 1H), 5.34 (s, 2H), 4.95 (d, J = 7.3 Hz, 1H), 3.83-3.77 (m, 1H), 3.55 ( s, 3H), 3.37 (s, 3H), 2.98-2.96 (m, 1H), 2.32 (s, 3H), 1.68-1.20 (m, 8H).

MS (ESI+) 415 ($M^+$+1, 100%)

The compounds of Embodiments 19 to 22 were synthesized from the various corresponding reference compounds using the same method as that in Embodiment 18.

Embodiment 19

1,3-dimethyl-7-(2-chloro-5-fluorobenzyl)-8-[(cis-2-aminocyclohexyl)amino]xanthine

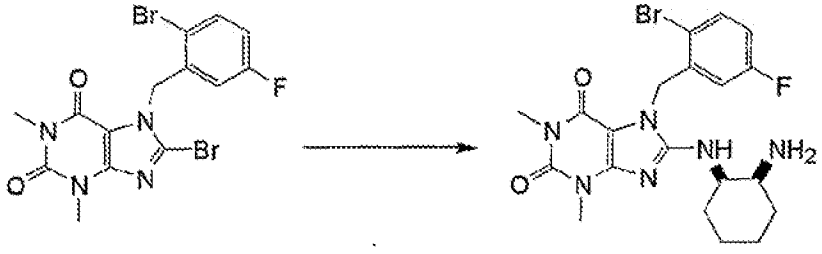



$^1$H NMR (400 MHz, $CDCl_3$) δ 7.38-7.35 (m, 1H), 6.98-6.93 (m, 1H), 6.79-6.76 (m, 1H), 5.44 (s, 2H), 5.13 (d, J = 7.2 Hz, 1H), 3.86-3.82 (m, 1H), 3.54 (s, 3H), 3.38 (s, 3H), 3.04-3.01 (m, 1H), 1.69-1.34 (m, 8H).

MS (ESI+) 435 ($M^+$+1, 100%)

Embodiment 20

1,3-dimethyl-7-(2-bromo-5-fluorobenzyl)-8-[(cis-2-aminocyclohexyl)amino]xanthine



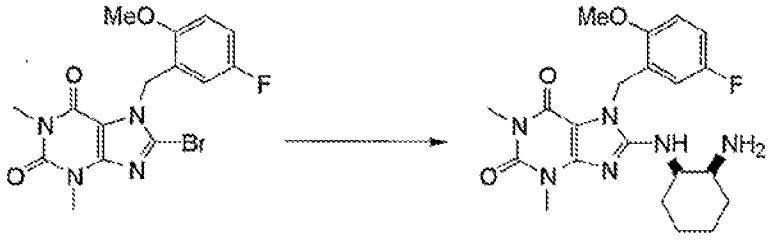

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.56-7.53 (m, 1H), 6.92-6.87 (m, 1H), 6.71-6.68 (m, 1H), 5.42 (s, 2H), 5.08 (d, J = 7.3 Hz, 1H), 3.86-3.82 (m, 1H), 3.55 (

s, 3H), 3.37 (s, 3H), 3.04-3.03 (m, 1H), 1.60-1.35 (m, 8H).

MS (ESI+) 479 ($M^+$+1, 100%)

Embodiment 21

1,3-dimethyl-7-(2-methoxy-5-fluorobenzyl)-8-[(cis-2-aminocyclohexyl)amino]xanthine

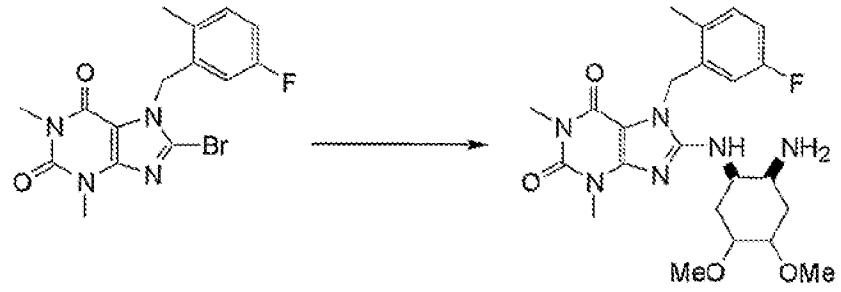



$^1$H NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (m, 1H), 6.99-6.94 (m, 1H), 6.87-6.84 (m, 1H), 5.63 (d, J = 7.4 Hz, 1H), 5.30 (s, 2H), 3.93 (s, 3H), 3.90-3.88 ( m, 1H), 3.49 (s, 3H), 3.41 (s, 3H), 3.16-3.14 (m, 1H), 1.64-1.38 (m, 8H).

MS (ESI+) 431 ($M^+$+1, 100%)

Embodiment 22

1,3-dimethyl-7-(2-methyl-5-fluorobenzyl)-8-[(cis-2-amino-4,5-dimethoxycyclohexyl)amino]xanthine

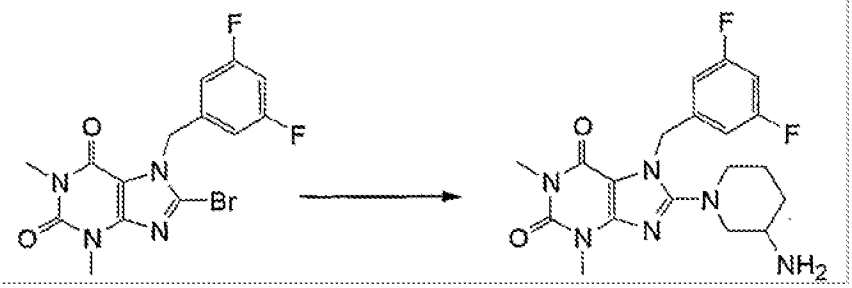



$^1$H NMR (400 MHz, $CDCl_3$) δ 7.17-7.13 (m, 1H), 6.90-6.86 (m, 1H), 6.51-6.42 (m, 1H), 5.40 (d, J = 17.1 Hz, 1H), 5.30 (d, J = 17.1 Hz, 1H), 4.95 (brs, 1H), 3.75-3.73 (m, 1H), 3.55 (s, 3H), 3.37-3.35 (m, 9H), 3.50-2.50 (m, 2H), 3.01-2.99 (m, 1H), 2.32 (s, 3H), 1.79-1.64 (m, 4H).

MS (ESI+) 475 ($M^+$+1, 100%)

Reference Example 1

1,3-dimethyl-7-(3,5-difluorobenzyl)-8-(3-aminopiperidin-1-yl)xanthine



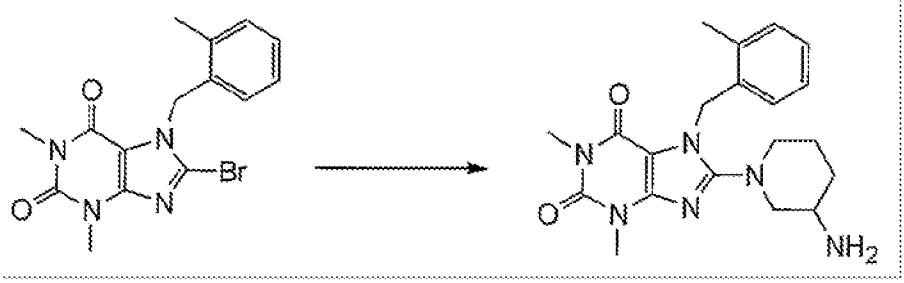
An ethanol solution (6 mL) of 1,3 dimethyl-7-(3,5-difluorobenzyl)-8-bromoxanthine (385 mg), 3-aminopiperidine (346 mg), and diisopropylethylamine (0.7 mL) was sealed in a tube, heated to 100°C and agitated for 25 hours. After cooling the reaction solution to 25°C, 1N hydrochloric acid was added and extraction with ethyl acetate was conducted. The aqueous solution was neutralized with 4N NaOH aqueous solution, and extraction with ethyl acetate was conducted. The organic layer was dried with anhydrous magnesium sulfate and filtered, and then vacuum concentration was conducted. The residue was rinsed with ethanol and dried, and Reference Example 1 (320 mg) was obtained as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$) δ 6.75-6.69 (m, 3H), 5.33 (s, 2H), 3.55 (s, 3H), 3.39-3.37 (m, 1H), 3.37 (s, 3H), 3.26-3.21 (m, 1H), 3.01-2.91 (m, 2H), 2.76-2.72 (m, 1H), 1.99-1.95 (m, 1H), 1.82-1.63 (m, 2H), 1.33-1.24 (m, 1H).

MS (ESI+) 405 ($M^+$+1, 100%).

Reference Example 2

1,3-dimethyl-7-(2-methylbenzyl)-8-(3-aminopiperidin-1-yl)xanthine



The compound of Reference Example 2 was synthesized from the corresponding

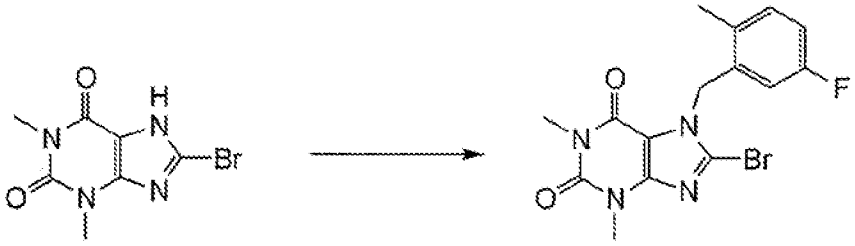
reference compound using the same method as that of Embodiment 6.

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.18-7.10 (m, 3H), 6.72 (d, J = 7.4 Hz, 1H), 5.38 (d, J = 16.5 Hz, 1H), 5.30 (d, J = 16.5 Hz, 1H), 3.57 (s, 3H), 3.39-3.35 (m, 1H), 3.34 (s, 3H), 3.28-3.24 (m, 1H), 2.94-2.84 (m, 2H), 2.72-2.67 (m, 1H), 2.36 (s, 3H), 1.90-1.87 (m, 1H), 1.68-1.66 (m, 1H), 1.59-1.56 (m, 1H), 1.27-1.21 (m, 1H).

MS (ESI+) 383 ($M^+$+1, 100%).

Reference Example 3

1,3-dimethyl-7-(2-methyl-5-fluorobenzyl)-8-bromoxanthine



5-fluoro-2-methylbenzylbromide (1.07 g) and potassium carbonate (0.76 g) were added to a dimethylformamide (20 mL) solution of 8-bromotheophylline (1.29 g) under nitrogen gas flow, and this was agitated for 20 hours at 25°C. Water (200 mL) was added to the reaction solution, and this was agitated for 1 hour. The deposited solid was separated and rinsed with hexane (100 mL), and the compound of reference example 3 (1.84 g) was obtained as a white solid.

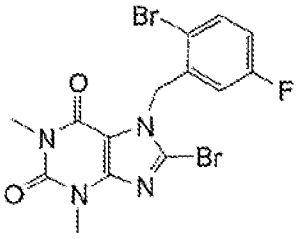
$^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.30-7.28 (m, 1H), 7.06-7.01 (m, 1H), 6.29-6.25 (m, 1H), 5.50 (s, 2H), 3.44 (s, 3H), 3.19 (s, 3H), 2.36 (s, 3H).

MS (ESI+) 381 ($M^+$+1, 100%).

The same method as that of Reference Example 3 was used to synthesize Reference Examples 4 to 9.

Reference Example 4

1,3-dimethyl-7-(2-bromo-5-fluorobenzyl)-8-bromoxanthine

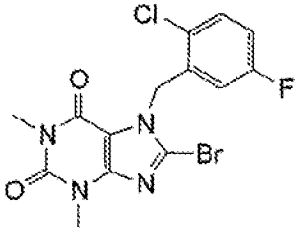


$^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.79-7.75 (m, 1H), 7.21-7.16 (m, 1H), 6.53-6.49 (m, 1H), 5.52 (s, 2H), 3.46 (s, 3H), 3.19 (s, 3H).

MS (ESI+) 445 ($M^+$+1, 47%).

Reference Example 5

1,3-dimethyl-7-(2-chloro-5-fluorobenzyl)-8-bromoxanthine

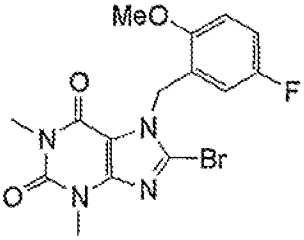


$^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.64-7.60 (m, 1H), 7.28-7.20 (m, 1H), 6.59-6.53 (m, 1H), 5.63 (s, 2H), 3.44 (s, 3H), 3.19 (s, 3H).

MS (ESI+) 401 ($M^+$+1, 61%).

Reference Example 6

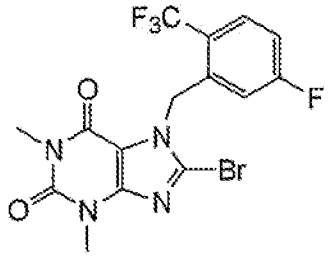
1,3-dimethyl-7-(2-methoxy-5-fluorobenzyl)-8-bromoxanthine



$^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.16-7.05 (m, 2H), 6.47 (dd, J = 2.9, 9.0 Hz, 1H), 5.44 (s, 2H), 3.85 (s, 3H), 3.43 (s, 3H), 3.19 (s, 3H).

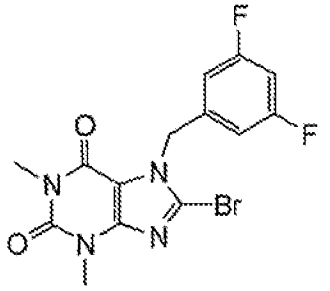
MS (ESI+) 397 ($M^+$+1, 100%).

Reference Example 7
1,3-dimethyl-7-(2-trifluoromethyl-5-fluorobenzyl)-8-bromoxanthine



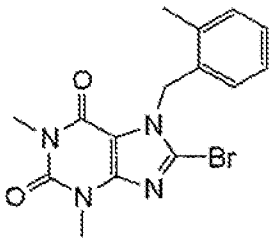
$^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.94 (dd, J = 5.4, 8.7 Hz, 1H), 7.42-7.38 (m, 1H), 6.64-6.61 (m, 1H), 5.71 (s, 2H), 3.46 (s, 3H), 3.19 (s, 3H).
MS (ESI+) 435 ($M^+$+1, 84%).

Reference Example 8
1,3-dimethyl-7-(3,5-difluorobenzyl)-8-bromoxanthine



$^1$H NMR (400 MHz, $CDCl_3$) δ 6.88-6.86 (m, 2H), 6.80-6.74 (m, 1H), 5.53 (s, 2H), 3.58 (s, 3H), 3.41 (s, 3H).

Reference Example 9
1,3-dimethyl-7-(2-methylbenzyl)-8-bromoxanthine

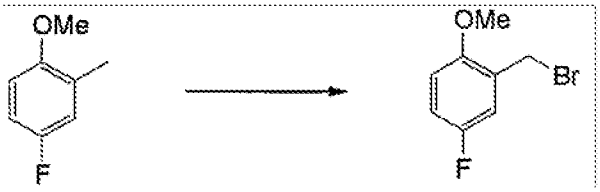


$^1$H NMR (400 MHz, $CDCl_3$) δ 7.23-7.18 (m, 2H), 7.12-7.08 (m, 1H), 6.47 (d, J = 5.8 Hz, 1H), 5.57 (s, 2H), 3.61 (s, 3H), 3.36 (s, 3H), 2.45 (s, 3H).

MS (ESI+) 363 ($M^+$+1, 94%).

Reference Example 10

5-fluoro-2-methoxybenzylbromide

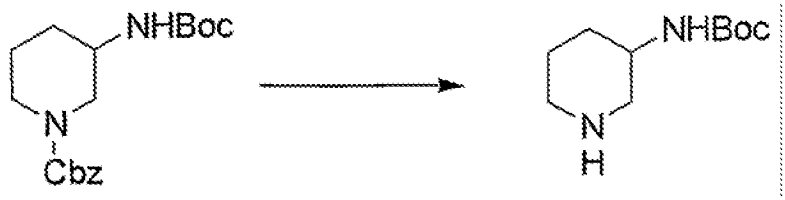



N-bromosuccinimide (1.96 g) and azobisisobutylonitrile (20 g) were added to a carbon tetrachloride solution (20 mL) of 4-fluoro-2-methylanisole (1.40 g) under nitrogen gas flow, and this was agitated for 19 hours at 80°C. After cooling the reaction solution to 25°C, and chloroform extraction was conducted by adding chloroform (100 mL) and 0.5% aqueous sodium carbonate solution. After the organic layer was dried with anhydrous sodium sulfate and filtered, vacuum concentration was conducted, and the compound of Reference Example 10 (2.34 mg) was obtained as a colorless fluid.

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.08-7.04 (m, 1H), 6.98-6.95 (m, 1H), 6.81 (dd, J = 4.3, 9.0 Hz, 1H), 4.50 (s, 2H), 3.87 (s, 3H).

Reference Example 11

3-[(tert-buthoxycarbonyl)amino]piperidine



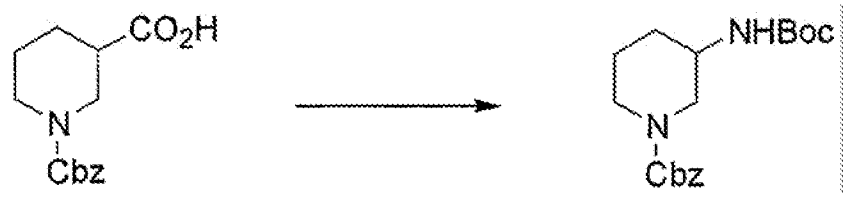

10% palladium-carbon (50% water content) (8.50 g) was added to a methanol solution (250 mL) of benzyl-3-[(tert-buthoxycarbonyl)amino]piperidin-1-carboxylate (11.69 g) and was agitated for 7 hours at 25°C under a hydrogen atmosphere. The catalyst was filtered out, and vacuum concentration was conducted on the organic layer. Saturated sodium bicarbonate water (100 mL) was added to the reaction mixture, and extraction was conducted twice with chloroform (50 mL). The organic layer was dried with anhydrous sodium sulfate and filtered, vacuum concentration was conducted, and the compound of Reference Example 11 (9.89 g) was obtained as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$) δ 3.60-3.53 (m, 1H), 3.07-3.04 (m, 1H), 2.85-2.78 (m, 1H), 2.70-2.62 (m, 1H), 2.56-2.48 (m, 1H), 1.84-1.79 (m, 1H), 1.70-1.66 (m, 1H), 1.51-1.47 (m, 2H), 1.44 (s, 9H).

MS (ESI+) 201 ($M^+$+1, 100%).

Reference Example 12

Benzyl-3-[(tert-buthoxycarbonyl)amino]piperidine-1-carboxylate




Triethylamine (6.20 mL) and then diphenylphosphorylazide (12.28 g) were added to a tert-butylalcohol solution (80 mL) of 1-[(benzyloxy)carbonyl]piperidin-3-carbonate (11.19 g) under nitrogen gas flow, and this was heated to 80°C and agitated for 10 hours. After cooling to 25°C, 5% potassium carbonate aqueous solution (100 mL) was added. After vacuum removal of the tert-butylalcohol, extraction was conducted twice on the remaining solution using chloroform (100 mL). The organic layer was dried with anhydrous sodium sulfate and filtered, and vacuum concentration conducted. The residue was refined by silica gel column chromatography (development solvent:

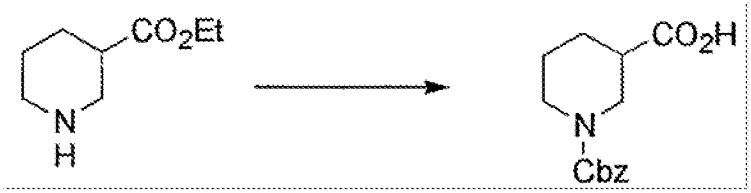
chloroform/methanol = from 20/1 to 3/1), and the compound of Reference Example 12 (9.89 g) was obtained.

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 5.16 (d, J = 12.5 Hz, 1H), 5.12 (d, J = 12.5 Hz, 1H), 4.63-4.55 (m, 1H), 3.75-3.65 (m, 1H), 3.52-3.45 (m, 1H), 3.36-3.25 (m, 2H), 1.90-1.82 (m, 1H), 1.72-1.65 (m, 1H), 1.59-1.50 (m, 2H), 1.43 (s, 9H).

MS (ESI+) 335 ($M^+$+1, 100%).

Reference Example 13

1-[(benzyloxy)carbonyl]piperidin-3-carboxylate

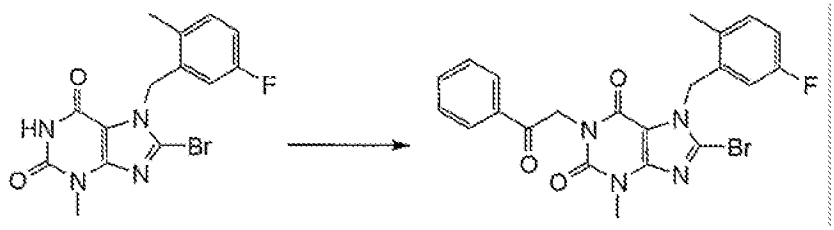



Triethylamine (14.86 mL) was added to a dichloromethane solution (300 mL) of ethyl nipecotinate (15.30 g); then benzyl chlorocarbonate (17.00 g) was instilled under nitrogen gas flow, and this was heated to 25°C and agitated for 6 hours. Water (100 mL) and 5% citrate aqueous solution (100 mL) were added to the reaction solution, and extraction was conducted twice using chloroform (100 mL). The organic layer was dried with anhydrous sodium sulfate and filtered, and vacuum concentration conducted. 1N sodium hydride aqueous solution (96 mL) was added at 0° C to an ethanol solution (200 mL) of the residue (18.63 g), and was agitated for 12 hours after raising the temperature to 25°C. After adding 2N hydrochloric acid to adjust the solution to pH=7, the ethanol was removed under reduced pressure. Potassium carbonate was added to adjust the remaining solution to pH=10, and extraction was conducted with diethyl ether. 2N hydrochloric acid was added to adjust the remaining solution to pH=2, and extraction was conducted twice with ethyl acetate (150 mL). The organic layer was dried with anhydrous sodium sulfate and filtered, vacuum concentration was conducted, and the compound of Reference Example 13 (14.54 g) was obtained as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 5.15 (d, J = 12.6 Hz, 1H), 5.11 (d, J = 12.4 Hz, 1H), 4.24-4.16 (m, 1H), 3.99-3.94 (m, 1H), 3.20-3.02 (m, 1H), 2.96-2.89 (m, 1H), 2.56-2.46 (m, 1H), 2.09-2.06 (m, 1H), 1.75-1.62 (m, 2H), 1.58-1.42 (m, 1H).

Reference Example 14

1-(2-oxo-2-phenylethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-bromoxanthine



Potassium carbonate (332 mg) was added to a dimethylformamide solution (10 mL) of 3-methyl-7-(2-methyl-5-fluorobenzyl)-8-bromoxanthine (734 mg) under nitrogen gas flow; and the solution was heated to 80°C and agitated for 1 hour. Next, a dimethylformamide solution (1 mL) of α-bromoacetophenone (332 mg) was instilled, and after instillation, this was heated and agitated for 8 hours at 80°C. The reaction solution was cooled to 25°C, water (100 mL) was added, and then hexane (100 mL) was also added. The deposited solids were filtered out and thoroughly dried at 50°C under reduced pressure; and the compound of Reference Example 14 (800 mg g) was obtained as a white solid.

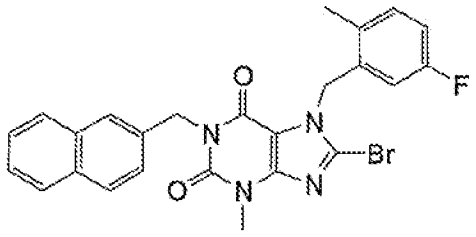
$^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.00-7.98 (m, 2H), 7.62-7.58 (m, 1H), 7.50-7.47 (m, 2H), 7.17-7.14 (m, 1H), 6.91-6.86 (m, 1H), 6.25-6.22 (m, 1H), 5.52 (s, 2H), 5.41 (s, 2H), 3.63 (s, 3H), 2.37 (s, 3H).

MS (ESI+) 485 ($M^+$+1, 100%).

The compounds of Reference Examples 15 to 20 were synthesized from the corresponding reference examples using the same method as that of Reference Example 14.

Reference Example 15

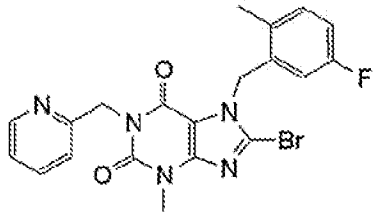
1-(2-naphthylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-bromoxanthine



$^1$H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.80-7.75 (m, 3H), 7.57-7.54 (m, 1H

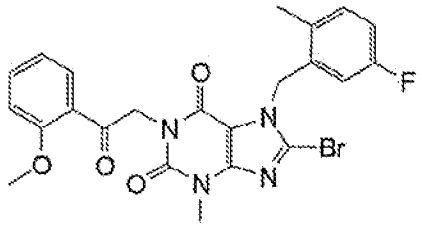
), 7.44-7.42 (m, 2H), 7.20-7.16 (m, 1H), 6.90-6.87 (m, 1H), 6.21 (dd, J = 2.5, 9.5 Hz, 1H), 5.54 (s, 2H), 5.30 (s, 2H), 3.60 (s, 3H), 2.40 (s, 3H).
MS (ESI+) 507 ($M^+$+1, 91%).

Reference Example 16
1-(pyridin-2-ylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-bromoxanthine



$^1$H NMR (400 MHz, $CDCl_3$) δ 8.50-8.49 (m, 1H), 7.63-7.59 (m, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.15 (m, 2H), 6.91-6.88 (m, 1H), 6.23 (dd, J = 2.6, 9.6 Hz, 1H), 5.54 (s, 2H), 5.29 (s, 2H), 3.62 (s, 3H), 2.36 (s, 3H).
MS (ESI+) 458 ($M^+$+1, 98%).

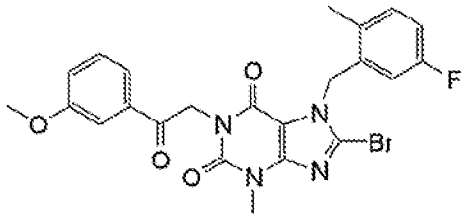
Reference Example 17
1-[2-oxo-2-(2-methoxyphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-bromoxanthine



$^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, J = 1.8, 7.8 Hz, 1H), 7.53-7.50 (m, 1H), 7.19-7.15 (m, 1H), 7.03-6.98 (m, 2H), 6.92-6.86 (m, 1H), 6.24 (dd, J = 2.6, 9.6 Hz, 1H), 5.52 (s, 2H), 5.35 (s, 2H), 3.94 (s, 3H), 3.62 (s, 3H), 2.36 (s, 3H).
MS (ESI+) 515 ($M^+$+1, 86%).

Reference Example 18

1-[2-oxo-2-(3-methoxyphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-bromoxanthine



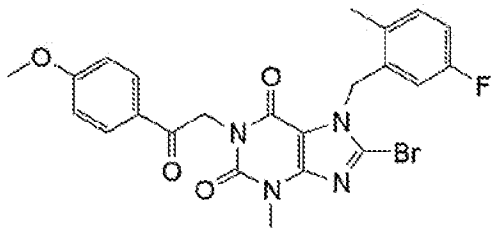
$^1$H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.8 Hz, 1H), 7.50-7.49 (m, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.17-7.13 (m, 2H), 6.91-6.88 (m, 1H), 6.25-6.22 (m, 1H), 5.52 (s, 2H), 5.39 (s, 2H), 3.84 (s, 3H), 3.63 (s, 3H), 2.37 (s, 3H)

.

MS (ESI+) 515 ($M^+$+1, 100%).

Reference Example 19

1-[2-oxo-2-(4-methoxyphenyl)ethyl]-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-bromoxanthine

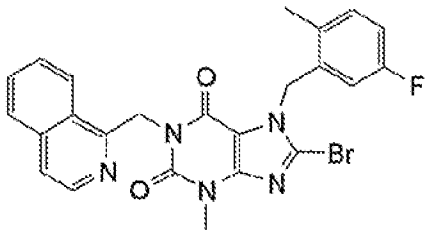


$^1$H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.9 Hz, 2H), 7.19-7.14 (m, 1H), 6.95 (d, J = 8.9 Hz, 2H), 6.91-6.87 (m, 1H), 6.24 (dd, J = 2.6, 9.5 Hz, 1H), 5.51 (s, 2H), 5.37 (s, 2H), 3.88 (s, 3H), 3.63 (s, 3H), 2.36 (s, 3H).

MS (ESI+) 515 ($M^+$+1, 91%).

Reference Example 20

1-(isoquinolin-1-ylmethyl)-3-methyl-7-(2-methyl-5-fluorobenzyl)-8-bromoxanthine

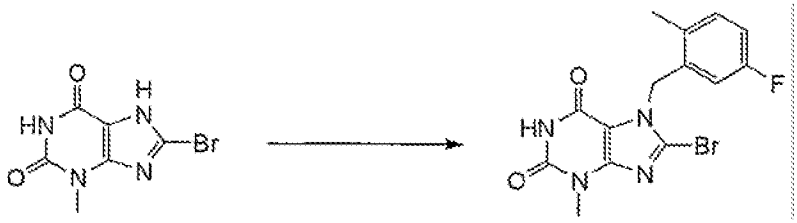


$^1$H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 5.7 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.67-7.61 (m, 2H), 7.50 (d, J = 5.7 Hz, 1H), 7.14-7.12 (m, 1H), 6.89-6.86 (m, 1H), 6.30 (dd, J = 2.5, 9.6 Hz, 1H), 5.82 (s, 2H), 5.54 (s, 2H), 3.66 (s, 3H), 2.34 (s, 3H).

MS (ESI+) 508 ($M^+$+1, 88%).

Reference Example 21

3-methyl-7-(2-methyl-5-fluorobenzyl)-8-bromoxanthine



5-fluoro-2-methylbenzylbromide (7.58 g) and hydrogen sodium carbonate (3.57 g) were added to a dimethylformamide solution (100 mL) of 3-methyl-8-bromoxanthine (8.71 g), and this was agitated for 20 hours at 25°C. Water (400 mL) was added to the reaction solution, and was agitated for 1 hour. The deposited solid was filtered out, rinsed with hexane (100 mL), and thoroughly dried under reduced pressure. The compound of Reference Example 21 (11.64 g) was obtained as a white powder.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.32 (s, 1H), 7.31-7.27 (m, 1H), 6.32-6.29 (m, 1H), 6.31 (dd, J = 2.6, 9.9 Hz, 1H), 5.46 (s, 2H), 3.36 (s, 3H), 2.35 (s, 3H).

MS (ESI+) 367 ($M^+$+1, 91%).

Test Example 1

Dipeptidylpeptidase inhibition action on dipeptidylpeptidase in bovine blood plasma

Bovine blood plasma containing dipeptidylpeptidase was diluted with assay buffer (25 mM Tris-HCl, 140 mM NaCl, 10 mM KCl, pH7.9), and 50 μL was added to a micro-assay plate. One micro liter of compound solution was added, mixed, and incubated at room temperature. Substrate (Glycyl-L-Proline 4-Methyl-Coumaryl-7-Amide, Peptide Laboratory) was diluted to 0.2 mM using assay buffer, and 50 μL was added. After agitating and incubating at room temperature, the reaction was stopped by adding 100 μL of 25% acetate aqueous solution. The fluorescent intensity at an excitation wavelength of 360 nm and a measurement wavelength of 460 nm was measured using a fluorescent plate feeder. The difference in fluorescent intensity between the background well in which the reaction was stopped in advance by adding 25% acetate aqueous solution prior to adding the substrate solution and the control well to which no compound was added was taken as 100%, and the fluorescent intensities of the compound added wells were calculated by interpolating and taking the residual enzyme activities when adding the compounds as relative values. The compound concentration to inhibit enzyme activity by 50% was calculated as the $IC_{50}$ value from the relative residual enzyme activity levels when adding compounds at multiple concentrations.

The compounds described in the embodiments and the comparative compound 1,3-dimethyl-7-(3,5-difluorobenzyl)-8-(3-aminopiperidin-1-yl)xanthine (reference example 1), which is the compound of the embodiment of WO 02/068420, were used in this test. The results are indicated in Table 18.

Table 18

| Compound | $IC_{50}$ (nM) | Compound | $IC_{50}$ (nM) |
|---|---|---|---|
| Compound of Embodiment 1 | 2.8 | Compound of Embodiment 14 | 4.6 |
| Compound of Embodiment 2 | 1.8 | Compound of Embodiment 15 | 18.9 |
| Compound of Embodiment 3 | 4.1 | Compound of Embodiment 16 | 15.1 |
| Compound of Embodiment 5 | 9.0 | Compound of Embodiment 17 | 210.0 |
| Compound of Embodiment 6 | 7.0 | Compound of Embodiment 18 | 12.1 |
| Compound of Embodiment 7 | 5.0 | Compound of Embodiment 19 | 9.4 |
| Compound of Embodiment 8 | 5.0 | Compound of Embodiment 20 | 12.2 |
| Compound of Embodiment 9 | 26.0 | Compound of Embodiment 21 | 84.0 |
| Compound of Embodiment 10 | 19.0 | Compound of Embodiment 22 | 61.4 |
| Compound of Embodiment 11 | 3.2 | Compound of Reference Example 1 | 74.4 |
| Compound of Embodiment 12 | 914.0 | | |
| Compound of Embodiment 13 | 69.5 | | |

Test Example 2

Dipeptidylpeptidase inhibition action in oral glucose tolerance tests in high fat diet fed mice

10-mL/kg solutions (1.0 μmol/kg as compound administered) of the compound of Embodiment 1 and the compound of Reference Example 2 (1,3-dimethyl-7-(2-methylbenzyl)-8-(3-aminopiperidin-1-yl)xanthine) (respectively prepared as 0.1 μmol/mL solutions by dissolving using a 0.5% carboxymethyl cellulose aqueous solution) were orally administered to high fat diet fed mice with induced obesity. A contrast group was administered the same dosage of 0.5% carboxymethyl cellulose aqueous solution. Thirty minutes after administering the test compounds and the 0.5% carboxymethyl cellulose aqueous solution, a 10-mL/kg dose of a solution of 0.2 g/mL glucose (2 g/kg as glucose administered) dissolved in physiological saline was orally administered. Blood was sampled from the caudal vein 15, 30, 60 and 120 minutes after the glucose load. The blood glucose levels (mg/dL) of the sampled blood were measured

using the Wako Glucose CII test (Wako Pharmaceutical Co.), and the area under curve (mg/dL•min) was calculated from the blood glucose levels at the various sample times up to 120 minutes after glucose load. (Here, the blood glucose level obtained from the sample prior to beginning the test was used as the blood glucose level at 0 minutes.)

The results are indicated in Table 19. The compound of Embodiment 1 significantly suppressed the rise in blood glucose level compared to the contrast group ($p=0.004$). Moreover, the compound of Embodiment 1 indicated a clearly superior effect to suppress the increase in blood glucose levels compared to the Reference Example 2.

Table 19

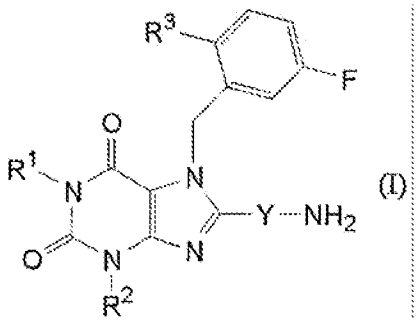
| | Mean value ± Standard deviation (mg/dL•min) |
|---|---|
| Contrast group | 27081±3235 |
| Compound of Reference Example 2 dosing group | 24117±3569 |
| Compound of Embodiment 1 dosing group | 20967±1097 |

Industrial Applicability

The present invention provides a compound having high DPP-IV inhibitory activity or is improved in safety, nontoxicity, etc.

# CLAIMS

1. A xanthine compound represented by the formula (I) below, a prodrug thereof, or a pharmaceutically permissible salt of either.




[In the formula, $R^1$ represents (1) a hydrogen atom, or (2) a $C_{1-6}$ alkyl group which may be substituted by one or multiple groups independently selected from $Ar^1$-X- or $A^1$;

$Ar^1$ represents an aryl group which may be substituted, an aromatic heterocyclic group which may be substituted, or an aliphatic heterocyclic group which may be substituted;

X represents a single bond, oxygen atom, -C(=O)-, -S(O)m-, or -S(O)m-NH-;

m represents 0, 1, or 2;

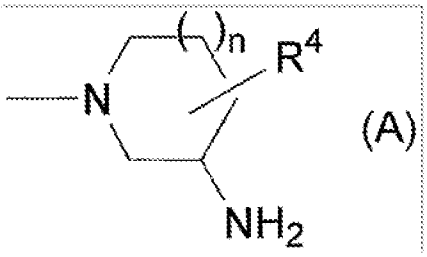
$A^1$ represents a halogen atom (which may be substituted with 1 to 3 of the same carbon atoms), hydroxyl group, oxo group, cyano group, carboxy group, carbamoyl group which may be substituted with 1 or 2 of the same or different $C_{1-3}$ alkyl groups, $C_{1-6}$ alkoxy group, amino group, $C_{1-6}$ alkylamino group, di-$C_{1-6}$ alkylamino group, hydroxyimino group, $C_{1-6}$ alkoxyimino group, acylamino group, $C_{1-6}$ alkoxycarbonylamino group, $C_{1-6}$ alkylthio group, $C_{1-6}$ alkylsulfinyl group, $C_{1-6}$ alkylsulfonyl group, $C_{1-6}$ alkoxycarbonyl group, arylsulfonyl group, $C_{3-6}$ cycloalkyl group, or $C_{1-6}$ alkylcarbonyl group;

$R^2$ represents a hydrogen atom, $C_{1-6}$ alkoxycarbonylmethyl group, or $C_{1-6}$ alkyl group;

$R^3$ represents a chlorine atom, bromine atom, iodine atom, cyano group, carboxy group, amino group which may be substituted, $C_{1-6}$ alkyl group which may be substituted,

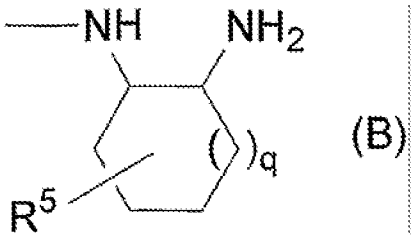
$C_{1-6}$ alkylthio group which may be substituted, $C_{1-6}$ alkylsufinyl group which may be substituted, $C_{1-6}$ alkylsulfonyl group which may be substituted, $C_{2-6}$ alkenyl group, $C_{2-6}$ alkynyl group, $C_{1-6}$ alkylcarbonyl group which may be substituted, $C_{1-6}$ alkoxy group which may be substituted, or a carbamoyl group which may be substituted;

-Y-$NH_2$ represents a group represented by formula (A) below:




(A)

(In the formula, n represents 0, 1 or 2; if 1 or 2 are present, $R^4$ represents an independent hydrogen atom, halogen atom, hydroxyl group, caboxy group, oxo group, amino group which may be substituted, $C_{1-6}$ alkoxy group which may be substituted, $C_{1-6}$ alkyl group which may be substituted, phenyl group which may be substituted, or benzyl group which may be substituted; or if 2 are present, $R^4$ represents methylene or ethylene together with the above, and a bridging ring may be formed by bonding with 2 carbon atoms comprising a ring.); or by formula (B) below:




(B)

(In the formula, q represents 0, 1 or 2; if 1 or 2 are present, $R^5$ represents an independent hydrogen atom, halogen atom, hydroxyl group, caboxy group, oxo group, amino group which may be substituted, $C_{1-6}$ alkoxy group which may be substituted, $C_{1-6}$ alkyl group which may be substituted, $C_{1-6}$ alkoxycarbonyl group which may be substituted, carbamoyl group which may be substituted, phenyl group which may be substituted, or benzyl group which may be substituted; or if 2 are present, $R^5$ represents methylene or ethylene together with the above, and a bridging ring may be formed by bonding with 2 carbon atoms comprising a ring.)]

2. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in Claim 1, wherein -Y-$NH_2$ is a group represented by formula (A) and n is 1 or 2, or -Y-$NH_2$ is a group represented by formula (B) and q is 1 or 2.

3. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in Claim 1, wherein -Y-$NH_2$ is a group represented by formula (A) and n is 1, or -Y-$NH_2$ is a group represented by formula (B) and q is 1.

4. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of Claims 1 to 3, wherein $R^2$ is a methyl group.

5. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of Claims 1 to 4, wherein $R^4$ or $R^5$ is a hydrogen atom, halogen atom, $C_{1-6}$ alkyl group which may be substituted, or $C_{1-6}$ alkoxy group which may be substituted.

6. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of Claims 1 to 5, wherein $R^3$ is a chlorine atom, bromine atom, iodine atom, methyl group, ethyl group, cyano group, trifluoromethyl group, methoxy group, trifluoromethoxy group, or difluoromethoxy group.

7. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of Claims 1 to 6, wherein $R^1$ is a $C_{1-6}$ alkyl group substituted by $Ar^1$-X-; $Ar^1$ is an aryl group which may be substituted, or an aromatic heterocyclic group which may be substituted; and X is a single bond, oxygen atom, -C(=O)-, or –S(O)m-.

8. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of Claims 1 to 6, wherein $R^1$ is a $C_{1-2}$ alkyl group substituted by $Ar^1$-X-; $Ar^1$ is an aryl group which may be substituted, or an aromatic heterocyclic group which may be substituted; and X is a single bond, or -C(=O)-.

9. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of Claims 1 to 6, wherein $R^1$ is an ethyl group substituted in position 2 by $Ar^1$-X-; $Ar^1$ is a phenyl group which may be substituted, a pyridyl group

which may be substituted, quinolyl group which may be substituted, or an isoquinolyl group which may be substituted; and X is a single bond.

10. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of Claims 1 to 6, wherein $R^1$ is a methyl group substituted by $Ar^1$-X-; $Ar^1$ is a phenyl group which may be substituted, a pyridyl group which may be substituted, quinolyl group which may be substituted, or an isoquinolyl group which may be substituted; and X is -C(=O)-.

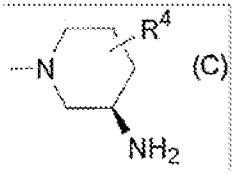
11. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of Claims 1 to 10, wherein $Ar^1$ is a phenyl group which may be substituted.

12. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of Claims 1 to 10, wherein $Ar^1$ is a pyridyl group which may be substituted.

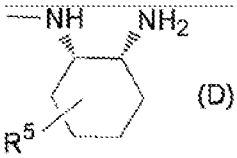
13. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of Claims 1 to 6, wherein $R^1$ is a hydrogen atom or a methyl group.

14. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of Claims 1 to 6, wherein $R^1$ is a methyl group.

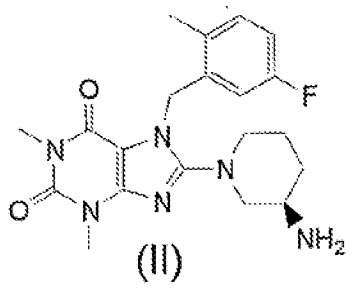
15. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of Claims 1 to 14, wherein $-Y-NH_2$ is the following formula (C).



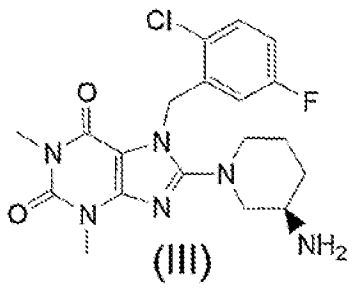

16. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of Claims 1 to 14, wherein $-Y-NH_2$ is the following formula (D).



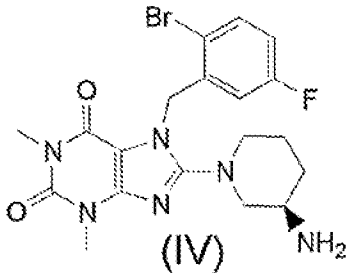
17. A xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in Claim 1 represented by formulae (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) below.



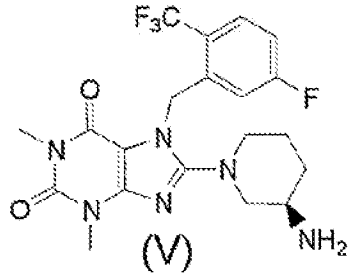

(II)



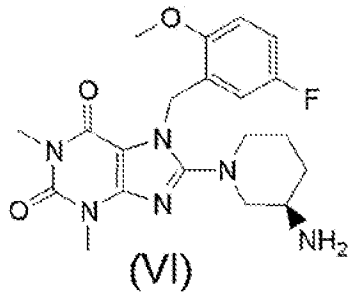

(III)



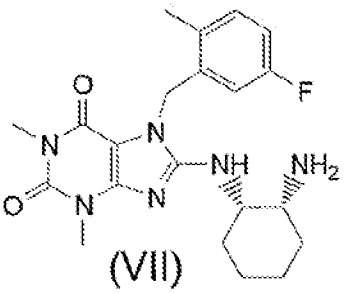

(IV)



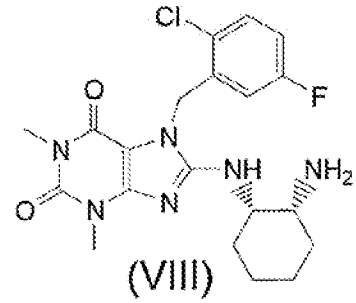

(V)



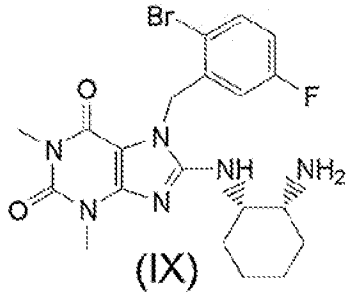

(VI)




(VII)




(VIII)




(IX)

18. A dipeptidyl peptidase IV inhibitor containing as an active ingredient the xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of Claims 1 to 17.

19. A diabetes therapeutic agent containing as an active ingredient the xanthine compound, a prodrug thereof, or a pharmaceutically permissible salt of either described in any of Claims 1 to 17.

20. A diabetes therapeutic agent described in Claim 19 for concomitant use with other diabetes therapeutic agents.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP03/13990

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D473/08, 473/06, A61K31/522, A61P3/10, 43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D473/08, 473/06, A61K31/522, A61P3/10, 43/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
REGISTRY(STN), CAPLUS(STN), CAOLD(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | WO 03/004496 A1 (NOVO NORDISK A/S), 16 January, 2003 (16.01.03), Particularly, examples 47, 74 & US 2003/0105077 A1 | 1-20 |
| A | WO 02/068420 A1 (BOEHRINGER INGELHEIM PHARMA KG.), 06 September, 2002 (06.09.02), & DE 10109021 A1 & EP 1368349 A1 & US 2002/0198205 A1 & NO 2003003726 A | 1-20 |
| A | WO 02/02560 A2 (NOVO NORDISK A/S), 10 January, 2002 (10.01.02), & JP 2004-502690 A & AU 2001068958 A & EP 1301187 A2 & BR 2001012123 A & US 2002/0161001 A1 & NO 2003000021 A & US 2004/0034014 A1 | 1-20 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 22 March, 2004 (22.03.04) | 13 April, 2004 (13.04.04) |
| Name and mailing address of the ISA/ Japanese Patent Office | Authorized officer |
| Facsimile No. | Telephone No. |

Form PCT/ISA/210 (second sheet) (July 1998)

| 国際調査報告 | 国際出願番号 PCT／JP03／13990 |
|---|---|

A. 発明の属する分野の分類（国際特許分類（IPC））

Int. Cl' C07D473／08, 473／06, A61K31／522, A61P3／10, 43／00

B. 調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

Int. Cl' C07D473／08, 473／06, A61K31／522, A61P3／10, 43／00

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

REGISTRY (STN), CAPLUS (STN), CAOLD (STN)

C. 関連すると認められる文献

| 引用文献のカテゴリー＊ | 引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示 | 関連する請求の範囲の番号 |
|---|---|---|
| PX | WO 03/004496 A1 (NOVO NORDISK A/S) 2003.01.16<br>特に、Example 47,74を参照。<br>& US 2003/0105077 A1 | 1－20 |
| A | WO 02/068420 A1 (BOEHRINGER INGELHEIM PHARMA KG) 2002.09.06<br>& DE 10109021 A1 & EP 1368349 A1 & US 2002/0198205 A1<br>& NO 2003003726 A | 1－20 |

☒ C欄の続きにも文献が列挙されている。　☐ パテントファミリーに関する別紙を参照。

＊ 引用文献のカテゴリー
「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

| 国際調査を完了した日 | 国際調査報告の発送日 |
|---|---|
| 22.03.2004 | 13.4.2004 |

| 国際調査機関の名称及びあて先 | 特許庁審査官（権限のある職員） | 4P | 9282 |
|---|---|---|---|
| 日本国特許庁（ISA／JP）<br>郵便番号100－8915<br>東京都千代田区霞が関三丁目4番3号 | 中木 亜希 | | |
| | 電話番号 03－3581－1101 内線 3492 | | |

様式PCT／ISA／210（第2ページ）（1998年7月）

| 国際調査報告 | 国際出願番号 PCT／JP03／13990 |
|---|---|

C（続き）． 関連すると認められる文献

| 引用文献のカテゴリー＊ | 引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示 | 関連する請求の範囲の番号 |
|---|---|---|
| A | WO 02/02560 A2 (NOVO NORDISK A/S) 2002.01.10<br>& JP 2004-502690 A & AU 2001068958 A & EP 1301187 A2<br>& BR 2001012123 A & US 2002/0161001 A1 & NO 2003000021 A<br>& US 2004/0034014 A1 | 1－20 |